Phase II study of bevacizumab in combination with capecitabine as first-line treatment in elderly patients with metastatic colorectal cancer

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The relative survival of elderly patients with metastatic colorectal cancer (mCRC) is generally worse than that of younger patients because of more advanced stage at presentation, comorbidity and reduced use of optimal therapy. We conducted a prospective phase II trial of the combination of bevacizumab and capecitabine in elderly patients with mCRC. In total 41 patients aged more than or equal to 70 years with mCRC, who had not received chemotherapy earlier for metastatic disease, were enroled. Patients received capecitabine (1000 mg/m^2 twice daily on days 1–14) and bevacizumab (7.5 mg/kg of body weight on day 1). The treatment cycles were repeated every 3 weeks. The overall response rate was 65%, including 13% of patients with a complete response and 53% of patients with a partial response. A further 13% of patients maintained stable disease. The median progression-free survival was 11.5 months and the median overall survival was 21.2 months. Despite the advanced age of participants, the rate of bevacizumab-related and capecitabine-related adverse events was consistent with that reported earlier in the general mCRC population. The combination of bevacizumab and capecitabine is effective and has a favourable tolerability profile and should be considered as an option for the initial treatment of mCRC in elderly patients. *Anti-Cancer Drugs* 22:191–197 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Colorectal cancer (CRC) is one of the most common malignancies, third after lung and prostate cancers in men and second only to breast cancer in women [1,2]. In Western countries CRC is the second leading cause of cancer death. Prognosis is generally poorest for the substantial proportion of patients with distant metastases, which may be present at diagnosis or may develop during the course of the illness [3].

The most important demographical risk factor for the development of CRC is the advancing age [1,2]. More than 70% of the CRC patients are more than 65 years old and more than 50% are over 70 years old, with a median age at diagnosis of 71 years [4]. The relative survival of elderly patients with CRC is generally poorer compared with younger patients. Although this may be partly explained by a tendency for older patients to present with more advanced disease, there is also evidence that elderly patients are less likely to be offered optimal therapy [5–7].

The management of elderly patients with CRC is challenging because of the high incidence of comorbidities (including diabetes and cardiac, renal, hepatic or pulmonary disease), the decreased haematopoietic reserve in older age, and age-related changes in the gastrointestinal system [8,9]. Furthermore, 40% of elderly patients with metastatic CRC (mCRC) have poor performance status [10]. As the population ages, the management of elderly patients with CRC is becoming an increasingly important clinical problem.

Elderly patients with mCRC seem to derive the same benefits from systemic chemotherapy as younger patients in terms of survival prolongation, symptomatic improvement and quality of life and experience a similar toxicity profile [11,12]. Nevertheless, older patients are greatly under represented in clinical trials of novel therapies. The median age of participants in the CRC chemotherapy study is approximately 60 years and, among the relevant trials of the CRC treatment, no more than 20% of the enroled patients are more than or equal to 70 years old [13,14]. As a result, there is a deficiency of good quality evidence on which clinical decisions for these patients are based.

Chemotherapeutic regimens based on 5-fluorouracil/leucovorin (5-FU/LV), either as monotherapy or in combination with other cytotoxic agents such irinotecan or oxaliplatin, have been shown to improve survival as first-line or second-line therapy for mCRC [15–23]. Intravenous 5-FU/LV is now being replaced by capecitabine, an orally administered fluoropyrimidine designed to deliver 5-FU directly to the tumour tissue [24,25]. Large scale, phase III trials have shown that capecitabine monotherapy is as effective as bolus 5-FU/LV and was well tolerated as first-line treatment for mCRC [26,27]. Capecitabine also showed noninferiority over 5-FU/LV in combination with oxaliplatin as first-line or second-line

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treatment for mCRC [28–30], and recent evidence supports similar efficacy of these two fluoropyrmidines when combined with irinotecan [31,32].

Bevacizumab is a targeted biological therapy that has shown efficacy in the first-line and the second-line treatment of mCRC when combined with single-agent or combination chemotherapy regimens [17–23]. As a recombinant humanized monoclonal antibody with a high binding specificity for vascular endothelial growth factor, bevacizumab induces regression of existing tumour microvasculature and inhibits the growth of new tumour vessels. Bevacizumab may also enhance the delivery of chemotherapy to the tumour by normalizing the tumour vasculature [33,34].

The established efficacy and favourable tolerability profiles of bevacizumab and capecitabine make this an attractive combination for mCRC treatment, especially for elderly patients who are often unsuitable for combinations of cytotoxic agents. Given the prevalence of mCRC among the elderly and the limited data regarding optimal therapy for these patients, we conducted a prospective phase II trial to evaluate the efficacy and safety of capecitabine plus bevacizumab as a first-line therapy for mCRC in patients more than or equal to 70 years old.

Methods

Patient eligibility

From June 2007 to November 2008, 41 patients aged more than or equal to 70 years old with inoperable mCRC that had not been treated earlier with chemotherapy were enroled at a single centre. Adjuvant chemotherapy, if administered, should have been completed at least 6 months before the enrolment in the trial. Patients were required to have histologically or cytologically confirmed colorectal adenocarcinoma and measurable disease, as defined by the presence of at least one lesion that is unidimensionally measurable (Response Evaluation Criteria in Solid Tumours criteria) by computed tomography scan [35]. Other inclusion criteria were Eastern Cooperative Oncology Group performance status 0–2 and life expectancy of at least 3 months.

The exclusion criteria included hypersensitivity to 5-FU or earlier severe reaction to fluoropyrimidines, history of other cancer in the previous 5 years (except for cured basal cell carcinoma of the skin or in-situ cervical carcinoma), treatment with other experimental drugs or radiotherapy within 4 weeks before the enrolment or recent major surgery from which the patient had not yet fully recovered. Patients were also considered ineligible if they had central nervous system involvement, neurological or psychiatric disorders that could interfere with the treatment compliance, significant cardiac disease or myocardial infarction in the earlier 12 months, serious uncontrolled infection, malabsorption syndrome, lack of physical integrity of the upper gastrointestinal tract or if they were organ allograft recipients. In addition, patients were not enroled if screening evaluations showed significant abnormalities in the neutrophil count ($< 1.5 \times 10^9$/l), platelet count ($< 100 \times 10^9$/l), serum bilirubin [> 1.5 times the upper limit of normal (ULN)], alanine transaminase, aspartate transaminase or alkaline phosphatase (> 2.5 times the ULN) or if the screening indicated inadequate renal function (creatinine clearance < 50 ml/min). Up to five times the ULN for alanine transaminase, aspartate transaminase and alkaline phosphatase was allowed for patients with liver metastases, and up to 10 times the ULN for alkaline phosphatase was permitted for patients with bone metastases.

All patients gave written informed consent in accordance with national legislation. The study adhered to the principles of the Declaration of Helsinki and the protocol was reviewed and approved by the Central Ethics Committee of Republic of Croatia.

Study treatment

Capecitabine was administered at a dose of 1000 mg/m^2 twice daily for 2 weeks followed by a 1-week rest period. The two daily doses of capecitabine were administered orally, 12-h apart, within 30 min of breakfast and evening meals. Each patient received a minimum of three 3-weekly cycles, unless the disease progression was detected. Patients with a complete response (CR), partial response (PR) or stable disease continued chemotherapy until progression or unacceptable toxicity. Chemotherapy could also be discontinued because of patient refusal or noncompliance, treatment delay of more than 2 weeks (except in the case of perceived patient benefit), or physician decision to discontinue the therapy. Patients were evaluated for adverse events before each cycle and were graded according to World Health Organization criteria [36]. For hand–foot syndrome, the standard published grading system was used [37]. Patients discontinuing capecitabine because of adverse events could continue to receive bevacizumab as monotherapy.

Bevacizumab was administered at a dose of 7.5 mg/kg of body weight on the first day of each 3-weekly cycle. The duration of the first bevacizumab infusion was 90 min. If the first infusion was well tolerated, the second infusion was administered over 60 min and, if this was well tolerated all subsequent infusions were administered over 30 min. The dose of bevacizumab was recalculated if the patient's bodyweight changed to more than 10% during the course of the study. Dose reduction of bevacizumab was not allowed. In cases of unacceptable toxicity predominately related to the administration of bevacizumab, bevacizumab could be withdrawn and the patient could be maintained on capecitabine monotherapy.

Assessments

The baseline evaluation included chest radiograph and/or chest computed tomography scan, abdominal and pelvic

computed tomography scan, bone scan (if indicated), demographics, medical history, physical examination, vital signs, Eastern Cooperative Oncology Group performance status evaluation, haematology, biochemistry, creatinine clearance, urine analyses, carcinoembryonic antigen testing and electrocardiography.

Symptom assessment, physical examination, haematology and blood biochemistry were repeated before each treatment cycle. Tumour measurements were taken every three cycles with the same technique used at the baseline assessment. The tumour response was determined according to the Response Evaluation Criteria in Solid Tumours criteria [35] and all responses required confirmation of a minimum of 4 weeks after they were first recorded. In most patients, the confirmation of response was expected to take place at the next planned tumour assessment (i.e. after 9 weeks).

Patients were closely followed, with examinations conducted at least bimonthly or more frequently if required. The time to progression was monitored and subsequent therapy was documented. Finally, overall survival was recorded.

Statistical methods

In combination therapies for mCRC, an overall response rate (ORR) of 50% or more can be considered encouraging, whereas a response rate of 30% merits less interest. To detect an expected increase in ORR from 30% (null hypothesis) to 50% with statistical power of 80% and α value of 0.05, a sample size of 40 patients was required.

The primary endpoint was ORR (CR + PR). Secondary endpoints were progression-free survival (PFS), overall survival and safety. PFS and overall survival were calculated using the Kaplan–Meier method. Descriptive statistics were used to analyse the characteristics of the patient.

Dose intensity was calculated for each patient from the total dose of capecitabine administered during the entire course of the treatment and expressed as the mean weekly drug dose (in g/m^2/week).

Safety parameters are presented as a percentage of total evaluable patients.

Results

Patients

Between June 2007 and November 2008, a total of 41 patients with mCRC aged more than 70 years were enroled in this single-centre study. The baseline characteristics of the patients are shown in Table 1. The mean age of participants was 75 years (range: 70–83 years). Overall, 26 patients (63%) presented with metastases at the time of diagnosis and 15 patients (37%) presented with metastases secondary to an earlier resected tumour (10 had primary stage II disease and five had primary stage III). In 34 patients (83%), the primary tumour was resected. Three patients (7%) had received adjuvant chemotherapy earlier, and two patients (5%) had been treated with radiotherapy. As expected for an elderly population, there was a high incidence of comorbid conditions (Table 2).

Treatment

A total of 534 cycles of treatment were administered, with a median of 12 cycles per patient (range: 2–30 cycles). Median cycle duration was 22.3 days (range: 21–69 days). One patient received fewer than three cycles of therapy (because of adverse events) and one patient refused to continue the treatment after four cycles. All 41 enroled

Table 1 Baseline characteristics of the patient

Characteristic	*N* (%)
Age (years)	
Mean	75
Range	70–83
70–75	24 (59)
76–79	12 (29)
$\geq$ 80	5 (12)
Sex	
Male	23 (56)
Female	18 (44)
ECOG performance status	
0	25 (61)
1	15 (37)
2	1 (2)
Location of primary tumour	
Colon	31 (76)
Rectum	6 (15)
Rectosigmoid	4 (10)
Grade of primary tumour	
1	9 (22)
2	16 (39)
3	12 (29)
No. of metastatic sites	
1	23 (56)
2	15 (37)
$\geq$ 3	3 (7)
Stage at diagnosis	
II	10 (24)
III	5 (12)
IV	26 (63)
Elevated CEA	33 (80)
Sites of metastasis	
Liver	32 (78)
Lung	16 (39)
Peritoneum	4 (10)
Lymph nodes	6 (15)
Adrenal gland	2 (5)
Earlier therapy	
Resection of primary tumour	34 (83)
Adjuvant chemotherapy	3 (7)
Adjuvant radiotherapy	2 (5)

CEA, carcinoembryonic antigen; ECOG, Eastern Cooperative Oncology Group.

Table 2 Patient's baseline comorbidities

Comorbid condition	*N* (%)
Hypertension	20 (49)
Diabetes	9 (22)
Atrial fibrillation	6 (15)
Ulcer disease	5 (12)
Hyperuricaemia	3 (7)
Benign prostatic hyperplasia	3 (7)
Osteoporosis	3 (7)

patients were considered assessable for safety and 40 patients were considered evaluable for efficacy.

Treatment delays were experienced by 21 patients (51%) during the course of the study, because of causes unrelated to the treatment (three patients), neutropenia (three patients) or nonhaematological adverse events (15 patients). Adverse events led to dose reductions in 24 patients (59%), most commonly for hand–foot syndrome, hyperbilirubinaemia or diarrhoea. The median dose intensity of capecitabine was 13.1 g/m^2/week, which is equivalent to 94% of the predicted dose intensity.

Poststudy therapy with irinotecan and/or oxaliplatin was received by 11 patients (27%). In two patients, PR during the study treatment permitted resection of residual disease after study completion. After surgery, one remained in complete remission and the other patient had progressive disease.

Tumour response and survival

The ORR was 65%, including five patients (13%) with a CR and 21 patients (53%) with a PR. A further five patients (13%) maintained stable disease, giving a disease control rate (CR + PR + stable disease) of 78%. Overall nine patients (23%) had progressive disease.

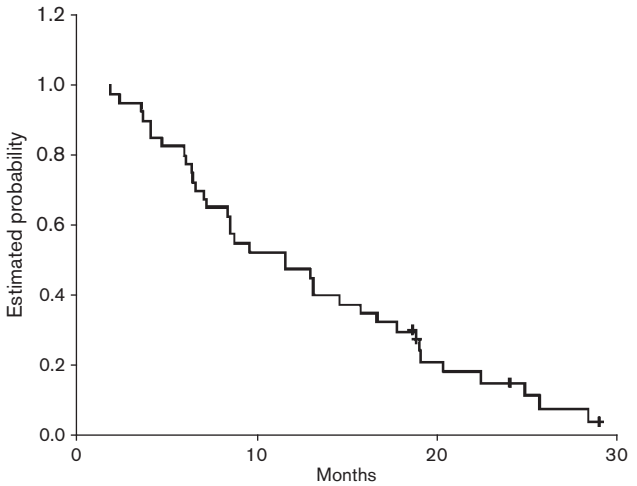
As of 15 February 2010, median duration of follow-up was 16.3 months. Overall, 36 patients (90%) had progressed with a median PFS of 11.5 months (range: 1.8–28.9 months; Fig. 1, Table 3). At the data cutoff, 21 patients (53%) had died and median overall survival was 21.2 months (range: 3.6–31.8 months; Fig. 2, Table 3).

Safety

Overall, 38 patients (93%) experienced treatment-related adverse events, the majority of which were grade 1/2 in intensity. The main treatment-related adverse events were hand–foot syndrome, arterial hypertension, proteinuria and hyperbilirubinaemia (Table 4). Treatment-related grade 3/4 adverse events occurred in 16 patients (39%) and included hand–foot syndrome (seven patients; 17%), deep vein thrombosis (five patients; 12%), arterial hypertension (three patients; 7%) proteinuria (two patients; 5%) fever (three patients; 7%) diarrhoea (one patient; 2%) and stomatitis (one patient; 2%). One patient (2%) had a myocardial infarction and one patient (2%) experienced bowel perforation.

Overall, two patients died while on therapy. One of these patients experienced sudden death during the seventeenth cycle and no autopsy was performed. The other death occurred during the second cycle, at another institution after recovery from grade-3 diarrhoea. Autopsy established lung oedema as the cause of death.

Fig. 1



Progression-free survival.

Table 3 Progression-free survival (PFS) and overall survival (OS)

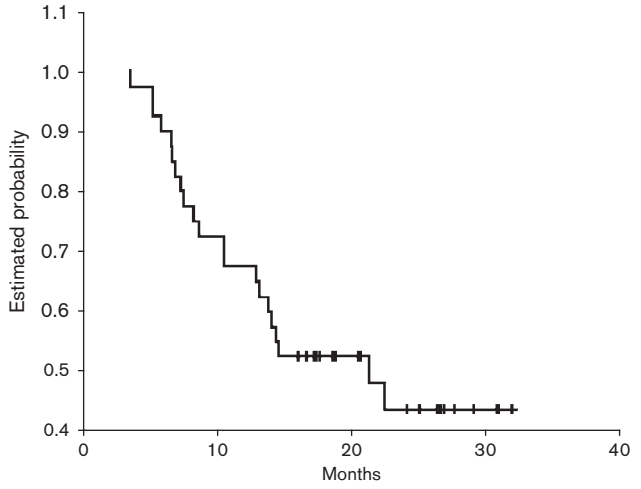
Endpoint (months)	Median (range)	Standard error	95% confidence interval	Lower quartile	Upper quartile
PFS	11.5 (1.8–28.9)	3.33	4.9–18.0	6.4	18.9
OS	21.2 (3.6–31.8)	5.97	9.5–32.9	8.3	–

Discussion

Today, the standard regimens for the treatment of mCRC have advanced beyond single-agent 5-FU/LV to combinations of fluoropyrimidines with oxaliplatin or irinotecan and bevacizumab, which have extended the median overall survival up to 24 months with the addition of bevacuzimab [15,16,38]. However, the decision to offer 'optimal' therapy necessitates careful consideration of the potential benefits in the context of the functional status of the patient, life expectancy, comorbidity, drug-specific toxicity and personal aspirations. These considerations are particularly relevant for the elderly population, in which the high rate of comorbidity increases the complexity of cancer management and affects survival [14]. Although elderly patients with good performance status derive a similar benefit from cytotoxic combinations as younger patients, they are usually treated with monotherapy regimens, that is, capecitabine or 5-FU/LV with or without bevacizumab [11,12].

Capecitabine first established its efficacy in mCRC as a single agent in the first-line treatment setting [26,27]. When compared with 5-FU/LV, capecitabine showed a significantly superior ORR (25.7 vs. 16.7%), even in patient subgroups with poor prognostic indicators, and at least equal effectiveness in terms of overall survival [26]. Capecitabine-treated patients experienced a significantly lower incidence of treatment-related diarrhoea, stomatitis, nausea, alopecia and grade 3/4 neutropenia and a higher rate of grade-3 hand–foot syndrome [26,27].

Fig. 2



Overall survival.

Table 4 Most common adverse events according to WHO criteria

	N (%)	
Adverse event	Grade 1/2[a]	Grade 3/4[b]
Haematological		
Neutropenia	7 (17)	0 (0)
Anaemia	14 (34)	0 (0)
Thrombocytopenia	17 (41)	0 (0)
Nonhaematological		
Hand–foot syndrome	26 (63)	7 (17)
Proteinuria	23 (56)	2 (5)
Arterial hypertension	20 (49)	3 (7)
Hyperbilirubinaemia	17 (41)	0 (0)
Diarrhoea	11 (27)	1 (2)
Fever	11 (27)	3 (7)
Loss of appetite	10 (24)	0 (0)
Fatigue	8 (20)	0 (0)
Nausea	7 (17)	0 (0)
Vomiting	6 (15)	0 (0)
Stomatitis	6 (15)	1 (2)
Tearing	6 (15)	0 (0)
Epistaxis	5 (12)	0 (0)
Nail changes	5 (12)	0 (0)
Deep vein thrombosis	0 (0)	5 (12)

WHO, World Health Organization.
[a]Includes all grade 1/2 adverse events occurring in more than 10% of patients.
[b]Includes all grade 3/4 adverse events, regardless of incidence.

In patients aged more than 70 years, capecitabine has been evaluated as first-line treatment for mCRC in two phase II studies. These trials showed ORRs of 24% and 13%, median PFS of 5.1 and 7 months and median overall survival of 16.3 and 11 months [39,40]. The treatment-related grade 3/4 adverse events occurred in 22% and 12% of patients [39,40].

The addition of bevacizumab to fluoropyrimidine chemotherapy in first-line treatment of mCRC increases ORR, prolongs time to progression and extends overall survival [17–22]. Pooled results from three phase II studies showed that the addition of bevacizumab to 5-FU/LV for earlier untreated mCRC increased overall survival from 14.6 to 17.9 months [18–20]. These encouraging phase II data prompted large-scale randomized phase III studies with bevacizumab plus either 5-FU/LV or capecitabine in combination with oxaliplatin or irinotecan [21–23,41]. All showed that bevacizumab, when added to first-line chemotherapy for mCRC, produces clinically meaningful improvements in efficacy [21–23]. The main adverse events associated with bevacizumab are thrombosis, hypertension, proteinuria and epistaxis [17–22].

In this study, the ORR with capecitabine plus bevacizumab was 65%, which is considerably higher than in earlier trials with capecitabine either alone [26,27,39,40] or in combination with bevacizumab [42]. Similarly, earlier studies have reported median PFS of 4.6–7 months with capecitabine monotherapy and 8.5 months with capecitabine plus bevacizumab [26,27,39,40,42], whereas our patient population achieved a median PFS of 11.5 months with the combination. This compares favourably with earlier trials with 5-FU/LV plus bevacizumab, which reported median PFS of 8.8 and 9.2 months [19,20].

At the data cut off, median overall survival in our population was 21.2 months. This compares very favourably with the median overall survival of 11 months reported in a study of first-line capecitabine in patients of more than oe equal to 70 years old and the 12.9 months achieved in a general mCRC population [26,40]. Indeed, the overall survival achieved by our patients was similar to that attained in the general mCRC population with bevacizumab plus capecitabine or bevacizumab plus 5-FU/LV (18.9 and 17.9 months, respectively) [20,42].

The impressive efficacy of capecitabine plus bevacizumab in this study might partly be attributed to the excellent compliance of our patients. Despite the advanced age of the participants, we achieved a median capecitabine dose intensity of 13.1 g/m^2/week, corresponding to 93.6% of the predicted dose intensity with a median of 12 cycles of therapy per patient. Other trials in similar patient populations have reported greater reductions in dose density and intensity [39,40].

Our trial enroled a high-risk patient population, with four in every five patients with at least one comorbidity and 41% of the patients exceeding the age of 75 years old. Nevertheless, the combination of capecitabine plus bevacizumab was well tolerated and we found no evidence for a higher rate of adverse events in this population. Adverse events attributed to capecitabine were similar to those reported in trials of capecitabine monotherapy [26,27,39,40]. We also noted that oral administration of capecitabine avoids the possible complications and discomfort of intravenous therapy, reduces the need for hospital visits and decreases interruption of daily activities [43,44]. Bevacizumab was generally well tolerated in combination with capecitabine. Adverse events were

mostly mild to moderate in intensity and manageable using the standard procedures. The incidences of all-grade hypertension, proteinuria, thromboembolism and bowel perforation were consistent with earlier studies of bevacizumab in first-line or second-line therapy in the general mCRC population [17–23].

Although combination chemotherapy regimens are generally considered more effective than single agents in the treatment of mCRC, it must be emphasized that many patients are not good candidates for such therapy. In particular, advanced age and associated comorbidities often preclude the use of cytotoxic combinations. Our results show that the combination of capecitabine plus bevacizumab as first-line therapy for elderly patients with mCRC is effective and has a favourable adverse event profile. This regimen should therefore be considered as an option for the initial treatment of mCRC in older patients.

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