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ORIGINAL ARTICLE

Capecitabine and bevacizumab in heavily pre-treated patients with advanced colorectal cancer

FINN OLE LARSEN, MOGENS KARSBØL BOISEN, ANNELENE L. FROMM & BENNY VITTRUP JENSEN

Department of Oncology, Herlev Hospital, University of Copenhagen, Denmark

Abstract

Background. No standard treatment exists for patients with metastatic colorectal cancer who have progressed after treatment with 5-fluorouracil (5-FU), oxaliplatin, irinotecan and an anti-EGFR antibody. The efficacy and safety of bevacizumab and capecitabine in heavily pre-treated patients with metastatic colorectal cancer were evaluated. *Patients and methods.* Patients with metastatic colorectal cancer, who had been exposed to 5-FU, oxaliplatin, and irinotecan in the first- and second line setting and mainly with irinotecan and cetuximab as third line treatment, were treated with capecitabine and bevacizumab. Four patients had received bevacizumab earlier. *Results.* From January 2009 to August 2010 34 patients started treatment with capecitabine and bevacizumab. The combination was well tolerated. Progression free survival was 5.4 months and median overall survival was 12.2 months. *Conclusion*. The combination of capecitabine and bevacizumab was safe with an acceptable toxicity profile and induced a significant rate of disease control in heavily pre-treated patients with metastatic colorectal cancer.

Bevacizumab is a humanized monoclonal antibody directed against vascular endothelial growth factor A (VEGF-A) [1]. Bevacizumab has shown efficacy in metastatic colorectal cancer (mCRC) in the first- and second line setting when used in combination with 5-fluorouracil (5-FU), irinotecan, and oxaliplatin [2–4]. Despite disease progression after treatment with irinotecan and an anti-EGFR antibody (cetuximab/panitumumab) in the third line setting, many patients maintain an excellent performance status, but so far, no treatment has been proven effective in this setting, and survival is short without further therapy. In two third line studies, the anti-EGFR antibodies cetuximab [5] and panitumumab [6] was compared to best supportive care (BSC), and in both studies a short progression free survival (PFS) of two months and a median overall survival (mOS) of about five months in the groups receiving BSC were found (Table I). Mono therapy with capecitabine does not seem to improve mOS [7], while 5-FU and bevacizumab seem to provide some improvement [8,9]. As the combination of capecitabine and bevacizumab is a well-tolerated regimen, easily manageable and with low toxicity; we offered the patients this regimen as salvage treatment.

Patients and methods

Pre-treated patients with histologically confirmed metastatic or inoperable colorectal cancer were treated with capecitabine 1000 mg/m^2 twice a day for two weeks followed by one week off together with bevacizumab 7.5 mg/kg every third week. As antiemetic 10 mg metoclopramide p.n. was used. Treatment was continued until disease progression or unacceptable toxicity. Toxicity was prospectively evaluated according to NCI-CTCAE, version 3.0 (www.cancer.gov). Tumor response was evaluated by a CT-scan of the thorax and abdomen every 12 weeks according to the RECIST criteria version 1.0 [10].

Treatment-, toxicity-, and efficacy data was gathered from patient records for this retrospective analysis. Survival data was retrieved from a national register using unique person registration numbers.

Progression free survival was calculated from the first administration of capecitabine and bevacizumab

Correspondence: F. O. Larsen, Department of Oncology, Herlev Hospital, Herlev Ringvej 75, DK-2730 Herlev, Denmark. Tel/Fax: + 45 40572246. E-mail: olelar02@heh.regionh.dk

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Table I. Historical data compared to our data.

Treatment	Median overall survival	Progression free survival	n	Reference
Best supportive care	4.6	2.0	285	5
	6.0*	1.8	232	6
Capecitabine	6.1	2.8	20	7
5-FU and bevacizumab	7.7	3.5	48	8
	9.0	3.5	350	9
Capecitabine and bevacizumab	12.2	5.4	34	

*Caution due to cross over.

to the first observation of disease progression or death from any cause. Overall survival (OS) was calculated from the first administration of capecitabine and bevacizumab to death from any cause, with censoring at January 2011. The Kaplan-Meier method was used to estimate the distribution of time to events for PFS and OS. Difference between survival curves was evaluated using the log-rank test. $P < 0.05$ was considered significant. All analyses were done using the statistical software package Graphpad Prism (GraphPad Software, Inc, La Jolla, CA, USA).

Results

Patient characteristics

Thirty-four patients started treatment with capecitabine and bevacizumab at our department from January 2009 to August 2010. All patients had been exposed to 5-FU, oxaliplatin, and irinotecan. Twenty-six patients, who were *KRAS* wild-type, had received and progressed on irinotecan and cetuximab, while eight patients who were *KRAS* mutated had not received cetuximab. Four patients had previously received bevacizumab and six patients had received sunitinib. One patient had received both bevacizumab and sunitinib, leaving nine patients who had prior anti-angiogenic therapy. Most of the patients were in performance status 0 (76%). Thirty-one (91%) had elevated carcinoembryonic antigen (CEA) at baseline and the median number of organs involved was two. The patient characteristics are outlined in Table II.

Toxicity

As seen in Table III, treatment was well tolerated with a low number of grade 3 and no grade 4 toxicities. The low incidence of toxicities found in this study was caused by the fact that all patients had received capecitabine earlier and we started them on an acceptable dose of capecitabine. Only hypertension was a common grade >2 toxicity (24%). None of the patients developed grade 3 or 4 bleeding, thrombosis or intestinal perforation.

Table II. Baseline characteristics (n = 34).

Median age, years (range)	65 (45–83)
Sex	
• Male/female	17/17
Performance status	
• 0	26
• 1	6
• 2	2
Location of primary tumor	
• Right colon (coecum to splenic flexure)	16
• Left colon (descending and sigmoid)	14
• Rectum	4
Previous treatment	
• 5-FU	34
• Oxaliplatin	34
• Irinotecan	34
• Cetuximab	26
• Sunitinib	6
• Everolimus	5
• Bevacizumab	4
Number of organs involved, median (range)	2 (1–4)
CEA (μg/l), median (range)	63.5 (0–39 361)

Efficacy

The median PFS was 5.4 months and the mOS was 12.2 months (Figure 1). Response rates according to RECIST criteria were as follows: no complete responses, three partial responses (9%), 21 stable diseases (62%), and 10 progressive diseases (29%). In univariate analysis, neither prior anti-angiogenic treatment, location of primary tumor, nor CEA level was associated with PFS or OS. Eight patients had no documented progression during prior treatment with a 5-FU containing regimen. They had either received 5-FU in an adjuvant treatment or had wanted a break after a long time on treatment and progressed during the break. A better outcome was observed for those eight patients versus the 24 patients with documented progression, (PFS 10.1

Table III. Toxicity.

	Grade 3	Grade 4
• Hypertension	8 (24%)	0
• Trombo-embolic events	1 (3%)	0
• Bleeding	1 (3%)	0
• Palmar-plantar erythrodysesthesia (PPE)	1 (3%)	0
• Diarrhea	0	0
• Nausea	0	0
• Fatigue	1 (3%)	0
• Neutropenia	1 (3%)	0
• Trombocytopenia	0	0

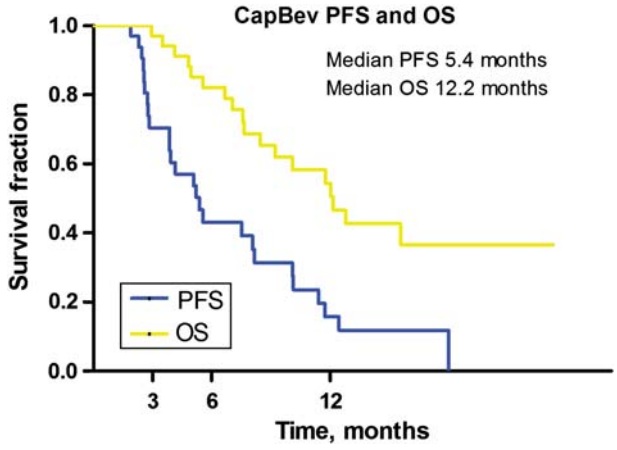

Figure 1. Progression free survival and overall survival to capecitabine and bevacizumab.

months vs. 5.1 months, not significant and mOS 19.5 months vs.10.1 months, p = 0.027).

Discussion

We found that the combination of capecitabine and bevacizumab in third or forth line was well tolerated and easily managed. Compared to historical data, this treatment seemed to offer attractive median PFS of 5.4 months and median OS of 12.2 months, which is much higher than other third line data, with best supportive care, where only a PFS of two months and mOS of five months were found [5,6]. We do not know if adding bevacizumab to chemotherapy is optimal in first line, or better used in later lines. When bevacizumab was added to FOLFOX in first line, Saltz et al. [4] could not show significant better mOS, which Giantonio et al. [2] did in second line. It would appear that monoclonal antibodies act different in patients that are chemotherapy naïve, compared to patients that are heavily pre-treated. While the exact explanation for this is unknown, several hypotheses have been postulated. One possibility is that exposure to chemotherapy induces adaptive changes in the cancer cell that increases it's receptability to EGFR and VEGFR directed antibody therapy possibly influencing their signaling pathways. Another possibility may be that the selected population who is still in a good condition to receive later line treatment is the same selected population that benefit from therapy with monoclonal antibody.

We found no difference in PFS or OS depending on whether or not the patients had received anti-angiogenic treatment before. On the other hand, we found a significant difference if the patients had progressed earlier on a 5-FU containing regimen. If patients had progressed on 5-FU, the median PFS was 5.1 months and median OS was 10.1 months, which is very similar to previous studies with 5-FU and bevacizumab [8,9]. If the patients had stopped 5-FU due to the patient's wish or after end of adjuvant treatment, the median PFS and OS were much higher (10.1 months and 19.4 months). This implies a great efficacy in reintroducing 5-FU to patients with tumors still sensitive to 5-FU.

In conclusion, we found that the combination of capecitabine and bevacizumab was well tolerated and easily managed and may induce a moderate rate of disease control in heavily pre-treated patients with metastatic colorectal cancer. The study further highlights the possible value of 5-FU re-introduction in patients without prior outright progression on this drug.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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