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LETTER TO THE EDITOR

Short time infusion of bevacizumab in combination with 5FU-based chemotherapy as first-line therapy in a non-selective patient group with metastatic colorectal cancer

LINE H. DOHN, BENNY V. JENSEN & FINN O. LARSEN

Department of Oncology, Herlev University Hospital, Herlev, Denmark

To the Editor,

Bevacizumab (BEV, Avastin) is a humanized recombinant monoclonal antibody which binds to and blocks the activity of all isoforms of vascular endothelial growth factor-A (VEGF-A), the key mediator of angiogenesis.

We wanted to find out if BEV given as a short time infusion in 10 minutes is feasible and to compare our data of overall survival (OS), progression free survival (PFS) and response rate (RR) as well as adverse events with data from previous trials [1–3].

In our retrospective study, patients with previously untreated colorectal cancer received [CapeOx] oxaliplatin 135 mg/m^2 as an intravenous infusion on day 1 followed by oral capecitabine 1000 mg/m^2 on day 1 through 14 of a 3-week cycle. Patients who had received oxaliplatin in adjuvant setting received [FOLFIRI]: irinotecan 180 mg/m^2 on day 1 with leucovorin 400 mg/m^2 administered as an intravenous infusion before 5-FU 400 mg/m^2 administered as an intravenous bolus injection, and 5-FU 2400 mg/m^2 as a 46-hour infusion immediately after 5-FU bolus injection, of af 2-week cycle. BEV was administered as a 10-minute intravenous infusion at a dose of 5 mg/kg on day 1 of a 2-week cycle when given with FOLFIRI or 7.5 mg/kg on day 1 of a 3-week cycle when given with CapeOx. Only patients in first-line treatment for metastatic colorectal cancer (MCRC) were included. Treatment was discontinued in the case of tumour progression, unmanageable grade 4 non-haematologic toxicity or at the request of the patient. BEV as single treatment was not allowed. Response to therapy was evaluated using the RECIST 1.0 criteria [4]. Response was evaluated every 12 weeks of treatment and the best response was noted.

Table I. Response and survival.

	Without Bevacizumab (n = 62)	With Bevacizumab (n = 75)
Response rate (CR + PR)	50%	41 %
Median PFS	8.2	9.6
CapeOx	8.4	9.2
FOLFIRI	7.6	10.8

The results were compared with a similar group of patients in our department who had received CapeOx or FOLFIRI in the period preceding implementation of BEV. Finally data were compared with data documented in previous clinical trials.

In the group treated with BEV response was observed in 31 of 75 patients (41%). In the group treated without BEV reponse was observed in 31 of 62 patients (50%). Two patients in each group exhibited CR.

The median PFS increased from 8.2 (8.4 for CapeOx and 7.6 for FOLFIRI) to 9.6 months (9.2 for CapeOx and 10.8 for FOLFIRI) when BEV was added to first-line chemotherapy (Table I). The median OS was not reached at the time data was analyzed.

Safety

BEV was given as a short time infusion in 10 minutes without any problems. The severe adverse events were similar to that seen in earlier trials (Table II). The incidence of high-grade venous thromboembolism was 5.3% associated with BEV and 4.8% in the control group. Patients treated with BEV had a non-significant increased risk of venous thromboembolism with a relative risk of 1.10 compared with controls. Suggesting

Correspondence: Line Hammer Dohn, Department of Oncology, Herlev University Hospital, Herlev Ringvej 75, DK-2730 Herlev, Denmark. E-mail: linehammer@hotmail.com

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Table II. Adverse events to bevacizumab.

Patients treated with BEV	IFL Hurwitz 2004 (n = 393)	E3200 Giantonio 2007 (n = 521)	NO 16966 Saltz 2008 (n = 694)	Herlev Dohn 2009 (n = 75)
Venous tromboembolic events (grade 3-4)				
with Bevacizumab	8.9%	3.4%	7.7%	(4/75)5.3%
without Bevacizumab	6.3%	2.5%	4.7%	(3/62)4.8%
Arterial tromboembolic events (grade 3-4)				
with Bevacizumab	na	0.9%	1.7%	0%
without Bevacizumab	na	0.4%	1.0%	0%
Major bleeding (grade 3-4)				
with Bevacizumab	3.1%	3.4%	1.9%	0%
without Bevacizumab	2.5%	0.4%	1.1%	0%
Gastrointestinal perforaton				
with Bevacizumab	1.5%	1%	0.6%	(1/75)1.3%
without Bevacizumab	0%	0%	0.3%	0%

a 10% greater risk for developing high-grade venous thromboembolism with BEV compared with controls. We observed one bowel perforation in the BEV treated patients which occurred 10 days after the first treatment. This patient was the only patient who died of a possible side effect to BEV. Other adverse events was hypertension, proteinuria and bleeding grade 1-2 which each occurred in about 30% of the BEV treated patients. These side effects were easily managed.

Discussion

Our patient group was not selected as in a protocol, but clinical data was similar in regard to gender, number of metastatic sites, location of primary tumor site and prior adjuvant therapy. The median age was slightly higher than seen in the randomized trials [1–3] as well as we had four patients in ECOG performance status 2. Even though our patients were not restrictively selected the PFS and RR of CapeOx + BEV and FOLFIRI + BEV were in line with the NO16966 trial [3]. The median OS was not reached at the time data was analyzed.

In our patient group the severe adverse events were similar to that found in earlier trials. In a large meta-analysis Nalluri et al. found that patients with colorectal cancer had a significantly increased risk of high-grade venous thromboembolism with a relative risk of 1.56 associated with BEV in comparison with control [5]. We did not see such strong correlation. We did not have any major bleeding and only a slightly increased risk of high-grade venous thromboembolism. We had one event with bowel perforation in the BEV treated patients which occurred 10 days after the first treatment. In the larger E3200 trial [2] six bowel perforations occurred in the BEV treated patients, with four of them after the first treatment. In the trials by Hurwitz, Giantonio, Saltz and our own study a total of 19 bowel perforations were seen, with 17 in the BEV treated patients. Bowel perforation is rare, but with six deaths out of 19, it makes it the most lethal side effect to BEV.

BEV is recommended given as a 90-minute infusion the first time, 60-minute the second time and here after 30-minute. As the anti-body is humanized, no allergic reaction is expected and it is well tolerated. To save time for the patients and the staff, we gave BEV as a 10-minute infusion. We had no infusion problems at any time.

The conclusion is that addition of BEV to either CapeOx or FOLFIRI is safe as a standard treatment to patients not enrolled in protocols and with similar side effects as seen in earlier trials. We also found that short time infusion of BEV given in 10 minutes is feasible and well tolerated.

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

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