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ORIGINAL ARTICLE

Bevacizumab-related arterial hypertension as a predictive marker in metastatic colorectal cancer patients

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Abstract
Purpose Patients with metastatic colorectal cancer (mCRC) receiving all three active drugs (irinotecan, oxaliplatin, fluorouracil) achieve the best outcome. Bevacizumab added to chemotherapy further improves progression-free (PFS) survival and overall survival. As arterial hypertension has been reported in all studies involving bevacizumab, we retrospectively analysed the correlation between the modifications of arterial blood pressure and response rate (RR) and PFS in mCRC patients treated with bevacizumab.
Patients and methods Patients with histologically proven mCRC receiving a first-line chemotherapeutic treatment were eligible. Arterial blood pressure was measured daily and hypertension graduated according to NCI-CTC V3.0 scale.
Results Seventy-four patients were considered for the present analysis; median age was 57 years (range 31–80). Sixty-seven patients had undergone surgery on primary tumour and, of these, 19 patients had formerly received adjuvant chemotherapy for stage II–III tumours. Chemotherapeutic regimens for metastatic disease were FOLFIRI (61 patients), FOLFOXIRI (6 patients), XELOX (5 patients) and XELIRI (2 patients). Eighteen patients (24.3%) had basal hypertension. Thirteen patients (17.6%) developed G2–G4 arterial hypertension. Six complete (8.1%) and 31 partial (41.9%) responses were recorded. Among patients with induced arterial hypertension, 84.6% achieved a complete or partial response, as compared with 42.6% of patients who did not show this side effect ($P = 0.006$). Kaplan–Meier analysis showed a statistically significant improvement in median PFS for patients with induced arterial hypertension (15.1 vs. 8.3 months, $P = 0.04$).
Conclusions Our data suggest that bevacizumab-related arterial hypertension may represent a predictive factor of response and prolonged PFS in patients with mCRC receiving first-line bevacizumab.

Keywords Bevacizumab · Arterial hypertension · Metastatic colorectal cancer · Predictive marker

Introduction

Colorectal cancer is the third most frequent tumour in both genders, with about 142,000 estimated new cases and 51,000 estimated deaths in 2010, in USA [1]. The 5-year survival of patients with metastatic disease is still poor (about 11%). However, in the last decade, the development of novel therapies targeting critical biological pathways of tumour cells has greatly expanded treatment options for patients with metastatic colorectal cancer (mCRC) and has shown substantial improvement in overall survival (OS) and progression-free survival (PFS).

Bevacizumab (Avastin; Genentech Inc., South San Francisco, CA) is a recombinant, humanized monoclonal antibody that binds to and neutralizes vascular endothelial growth factor (VEGF), a key mediator in angiogenesis [2].

In randomized trials enrolling patients with mCRC in first-line treatment, bevacizumab improved response rates (RR), OS and PFS when combined with the standard

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chemotherapy treatments containing 5-fluorouracil/leucovorin (5-FU/LV) [3] or irinotecan plus 5-FU/LV (IFL) [4]. In addition, the combination of bevacizumab with FOLFOX or capecitabine plus oxaliplatin (XELOX) resulted in significantly improved PFS compared with chemotherapy alone [5]. Moreover, promising results were reported by the association of bevacizumab with the triple combination of 5FU, oxaliplatin and irinotecan (FOLFOXIRI) [6].

In the second-line treatment of mCRC, patients who received bevacizumab in combination with FOLFOX4 regimen had an OS time that was two months longer than that of patients treated with FOLFOX4 alone [7].

Bevacizumab has a favourable safety profile: it does not exacerbate the toxicity associated with chemotherapy, and its side-effect profile is well defined and does not overlap with those of chemotherapeutic agents. The most common side effect of bevacizumab, arterial hypertension, is generally easily manageable with standard oral anti-hypertensive medication and does not usually require interruption of treatment. Minor muco-cutaneous bleeding events such as epistaxis are also common with bevacizumab but are curable using standard first aid techniques; the incidence of asymptomatic proteinuria is also increased, but symptomatic events are uncommon and occur at a similar incidence with chemotherapy and chemotherapy plus bevacizumab [8].

Arterial hypertension is the most common side effect registered in the trials of bevacizumab plus chemotherapy, with an overall incidence of 22–32% and grade 3/4 events in 11–16% of patients with metastatic CRC [3, 4]. In the safety analysis of the BEAT trial, 30% of patients experienced arterial hypertension of any degree [9]. In the randomized phase II trial of bevacizumab plus 5-FU/LV versus 5-FU/LV alone in patients with previously untreated metastatic CRC, grade 3/4 arterial hypertension was not seen in patients treated with 5-FU/LV alone but occurred in 3 of 35 patients treated with bevacizumab at the 5 mg/kg dose level and in 8 of 32 patients treated at the 10 mg/kg dose level [3]. These data suggest a possible dose relationship. In the randomized phase III trial of bevacizumab 5 mg/kg every 2 weeks plus IFL versus IFL alone, grade 3 arterial hypertension occurred in 11.0% of patients in the bevacizumab arm compared with 2.3% in the control arm [5]; similarly, in the phase II trial of first-line 5-FU/LV with or without bevacizumab in patients unsuitable for irinotecan therapy, the incidence was 16.0%, compared with 3% in the control arm [3]. These data suggest that at the widely used dosage of bevacizumab in colorectal cancer patients (5 mg/kg), the incidence of grade 3/4 hypertension is approximately 10–15%.

The incidence of arterial hypertension has already led Maitland et al. [10] to propose that elevation of blood pressure could be used as a biomarker for the activity of anti-angiogenetics on VEGF signal pathway.

The mechanism underlying bevacizumab-related hypertension is not yet clearly understood. As far as, endothelial dysfunction and micro-vascular rarefaction are hallmarks in all forms of arterial hypertension.

Vascular endothelial growth factor has been shown to enhance the activity of endothelial nitric oxide synthase (eNOS) and up-regulates the message and protein levels of VEGF receptor in endothelial cells. Nitric oxide (NO) plays an important role in the vascular homoeostasis, including the vasomotor tone and the balance between proliferative and apoptotic processes in the normal and pathological vessels. eNOS has been implicated in tumour angiogenesis and the maintenance of vasodilatation in tumour blood vessels, and the role of NO in tumorigenesis have been widely investigated. The therapeutic blockade of VEGF by bevacizumab inhibits the NO pathway and then endothelial function. A constant finding in both experimental induced and clinical idiopathic hypertension has been the micro-vascular rarefaction, defined as a reduced spatial density of micro-vascular networks [11, 12]. Because micro-vessels (arterioles and capillaries) are a major contributor (>90%) to total peripheral vascular resistance, functional rarefaction (a decrease in perfused micro-vessels) or anatomic rarefaction (a reduction in capillary density) may play an important role in the development of hypertension. Under physiological resting conditions, a substantial part of micro-vascular networks of most organs remains closed, constituting a flow reserve for adaptation to increased metabolic needs. It was first noted that hypertensive patients had an abnormally low number of small conjunctival vessel [13, 14]. Using venous occlusion capillaroscopy, the nail-fold capillary density was also reported to be significantly lower (by 10%) in non-diabetic patients with never-treated essential hypertension than in healthy normo-tensive control subjects matched for age, sex and lipid profile [15]. The reduction in capillary density was shown in patients treated with bevacizumab too.

The efficacy of most of the monoclonal antibodies used in the treatment of solid tumours has been correlated with the amount of the target (HER2-trastuzumab) [16, 17], with the presence of mutations that activate the intracellular pathway (KRAS—cetuximab) [18] or with the occurrence of specific side effects (cutaneous toxicity—cetuximab) [19]. The efficacy of bevacizumab has not been related to any particular biomarker, nor any predictive mutation of the VEGF or VEGFR has been characterized.

In the present study, we investigated the correlation between bevacizumab-related hypertension and RR, PFS and OS in metastatic colorectal patients who undergo treatment with bevacizumab plus chemotherapy.

Patients and methods

In our retrospective analysis, we considered histologically confirmed, chemo-naive mCRC patients, treated at our Department from November 2005 to June 2010 with first-line chemotherapy plus bevacizumab.

At baseline, all patients should have performed a complete screening of cardio-circulatory system (ECG, echocardiography, cardiologic examination) and a whole-body contrast-enhanced CT scan describing and measuring target lesions; at least four weeks should elapse between major surgery and the administration of bevacizumab.

Treatment

The regimen of chemotherapy associated with bevacizumab could be FOLFIRI, FOLFOX, XELOX, XELIRI and FOLFOXIRI. Bevacizumab was administered at the dose of 5 mg/kg if combined with FOLFIRI/FOLFOX/FOLFOXIRI and at the dose of 7.5 mg/kg if administered with tri-weekly schedules (XELOX/XELIRI).

All metastatic lesions had to be re-staged every 8 weeks and evaluated according to RECIST criteria. Chemotherapy was administered until progression of disease, unacceptable toxicity, refusal by the patient and, anyway, for a maximum of 6 months. Bevacizumab was discontinued in case of progression of disease, unacceptable toxicity or refusal by the patient; otherwise, it was continued, even after the 6 months of chemotherapy, until disease progression.

Arterial blood pressure measurement was taken before, during and after each administration of bevacizumab, and daily, between a cycle and the following one. A digital blood pressure reader was used for monitoring values.

Bevacizumab-related arterial hypertension was evaluated according to NCI—CTCAE 3.0. Grade I is an asymptomatic transient (<24 h) increase greater than 20 mm Hg (diastolic) or greater than 150/100 mm Hg if previously within normal limit, and no intervention is indicated; grade II, recurrent or persistent (>24 h) or symptomatic increase greater than 20 mm Hg (diastolic) or greater than 150/100 mm Hg if previously within normal limit, and mono-therapy may be indicated; grade III, requiring more than one drug or more intensive therapy than previously; and grade IV, hypertensive crisis.

Statistical methods

The categorical variables considered for statistical analysis were "responder" (complete and partial response) and "not responder" (stable disease and progressive disease) patients and without or with bevacizumab-related hypertension (new event or worsened pre-existing hypertension).

The correlation between categorical variables was estimated by chi-square test. Survival distribution was estimated by the Kaplan–Meier method. Significant differences in probability of relapsing between the strata were evaluated by log-rank test.

Overall survival and progression-free survival were defined, respectively, as the interval between the start of bevacizumab therapy and death or last follow-up visit and as the interval between the start of bevacizumab therapy and the clinical progression or death or last follow-up visit if not progressed.

A P level ≤ 0.05 was considered to assess the statistical significance.

Statistical analysis was carried out with SPSS software, version 18 (SPSS, Inc. Chicago, IL).

Results

A detailed summary of patients' characteristics is shown in Table 1. Seventy-four patients (42 men, 32 women) were analysed, with a median age of 57 years (range 31–80 years). Fifty-two patients (60.3%) were affected by metastatic colon cancer, and 22 patients (29.7%) had metastases from rectal disease. Sixty-seven patients had undergone resection of the primary neoplasm; among them, 23 patients were diagnosed a stage II or III colon/rectal cancer and 19 of them were submitted to adjuvant chemotherapy (9 patients received FOLFOX-4, 4 patients 5-FU/LV and 6 patients 5-FU/LV and radiotherapy). Fifty-one patients were in stage IV at diagnosis. The median time to recurrence of the 18 early-stage patients was 13 months (range 2–72 months).

Metastatic lesions were localized mostly at liver (38 patients), lung (11 patients), or both sites (11 patients). Overall, 15 patients (20.2%) had multiple sites of disease.

Bevacizumab was administered with FOLFIRI regimen in 61 cases; 6 patients received FOLFOXIRI, 5 XELOX and 2 XELIRI schedule.

Eighteen patients were already affected by pharmacologically controlled hypertension and had normal blood pressure levels when began bevacizumab plus chemotherapy.

The median duration of bevacizumab administration was 7 months (range 1.4–40.5 months).

All patients were evaluated for response. We registered 6 complete responses (8.1%) and 31 partial remissions (41.9%). Thirty-one patients (41.9%) obtained a stable disease and 6 of them (8.1%) a progression of disease. Thus, according to the classification described in "Patients and methods" section, we got 37 responder patients and 37 not responders.

Bevacizumab-related arterial hypertension occurred in 13 patients (17.6%): 1 grade 4, 1 grade 3, 11 grade 2.

Table 1 Patients' characteristics

	Patients with bevacizumab-related hypertension	Patients without bevacizumab-related hypertension	*P*
M/F	8/5	34/27	
Age at diagnosis (range)	56 (31–80)	60 (46–73)	
Primary tumour (colon/rectum)	6/7	46/15	
Medical history of arterial hypertension	3 (23%)	15 (24.5%)	
Anti-hypertensive treatment			
Diuretics/beta-adrenoceptor blocking drugs	1 (7%)	8 (13.1%)	
ACE inhibitors	2 (15.4%)	7 (11.4%)	
Previous adjuvant chemotherapy	1 (7%)	18 (29.5%)	
Sites of metastasis (%)			
Liver	7 (53.8%)	31 (50.8%)	
Lung	1 (7%)	10 (16.4%)	
Peritoneum		3 (4.9%)	
Nodes		3 (4.9%)	
Liver + lung	4 (30.7%)	7 (11.6%)	
Liver + peritoneum	1 (7%)	1 (1.6%)	
Liver + bone		1 (1.6%)	
Lung + brain		1 (1.6%)	
Local		2 (3.3%)	
Pelvis		2 (3.3%)	
Median duration of treatment (months)	10	7	
Treatment schedule			
FOLFIRI	11 (84.6%)	50 (82%)	
XELOX	1 (7.7%)	4 (6.5%)	
XELIRI		2 (3.2%)	
FOLFOXIRI	1 (7.7%)	5 (8.2%)	
Response rate (%)	11/13 (84.6%)	26/35 (42.6%)	0.01
Median PFS (months)	15.1	8.3	0.04
Median OS (months)	35.5	26.7	

Hypertension occurred in 1 of 13 patients already treated for hypertension (7.7%). The median time of development of hypertension was 63 days (range 1–365 days).

The correlation between arterial hypertension and response to treatment is reported in Table 2: 84.6% of the patients who experienced bevacizumab-related hypertension were responders (1 complete and 10 partial remissions) as compared with 42.6% of non-hypertensive patients ($P = 0.006$).

After a median follow-up period of 17.6 months (range 3.2–47.9 months), 57 patients (77%) progressed and 23 of them (40.4%) died.

Overall median PFS was 9.7 months (range 6.9–12.5 months). Patients who developed arterial hypertension showed a significantly longer median PFS (15.1 months; range 9.8–20.3 months) as compared with patients without hypertension (8.3 months; range 6.5–10.1 months), and this difference was statistically significant ($P = 0.04$) (Fig. 1).

The overall median observed OS was 35.5 months (range 24.5–46.5 months). In patients with bevacizumab-related hypertension, the median OS was 35.5 months (range 28–43 months) and it was 26.7 months (range 14.0–50.1 months) for the others ($P = 0.2$).

Table 2 Correlation between hypertension and response

	Bevacizumab hypertensive patients	Bevacizumab not hypertensive patients
Responders	11 (84.6%)	26 (42.6%)
Not responders	2 (15.4%)	35 (57.4%)
	13 (100%)	61 (100%)

$\chi^2 = 7.559$; $P = 0.006$

Discussion

Biological agents for the treatment of metastatic colorectal cancer (anti-EGFR monoclonal antibodies—cetuximab and panitumumab, or anti-VEGF monoclonal antibody—bevacizumab) are defined "targeted-therapy" drugs as they

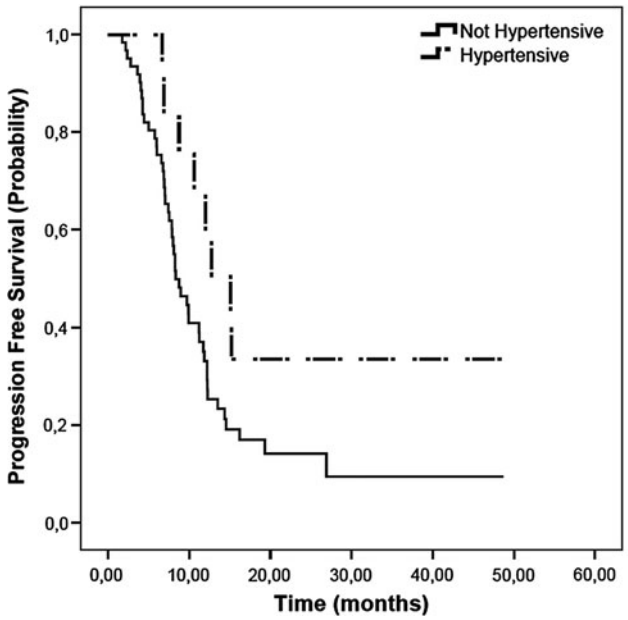

Fig. 1 Median PFS of patients with (*dotted lines*) and without (*solid lines*) bevacizumab-related arterial hypertension

inhibit cell proliferation by the direct action on specific molecular pathways of the tumour cells.

However, they are not effective in all patients, although cancer cells express the molecular targets fit for their action. Thus, the clinical research of the past five years focused on the study of molecular or clinical markers that can predict the activity of biological drugs in order to tailor the treatment of patients with metastatic colorectal cancer.

The use of EGFR inhibitors has been restricted to patients whose tumours express a wild type of k-ras gene, because its clinical benefit has been retrospectively found to be limited to this subgroup of patients [20, 21]. Moreover, some evidences suggest that the development of a grade $\geq$3 cutaneous rash following the administration of cetuximab is a predictive marker of a better outcome in colorectal [19–22] and in head and neck tumours [23].

In our retrospective analysis, we observed that 13 patients experienced G2–G4 arterial hypertension and, among them, 11 cases reported a clinical response. Moreover, median PFS was significatively better for those patients with bevacizumab-related hypertension. Thus, we postulated that arterial hypertension may represent a predictive clinical biomarker for the efficacy of bevacizumab.

Our data align those obtained by similar retrospective analyses. Scartozzi et al. [24] reported a statistically significant correlation between hypertension occurred during treatment with bevacizumab and PFS (14.5 months vs. 3.1 months $P = 0.04$) and RR (75% vs. 32% $P = 0.04$). In this study, the overall incidence of hypertension was 20%, which is very similar to our one (17%), although data collection was slightly different from our modality of measurement.

Furthermore, our data seem to be in agreement with other studies on different anti-angiogenic drugs, such as sorafenib, or sunitinib [10, 25]. Maitland, in a study on renal cancer patients treated with sorafenib, registered blood pressure values prior the beginning of therapy and after the steady-state plasma concentration of sorafenib has been reached (days 6–10). He found that both systolic and diastolic values were significantly higher at day 6 or 10 with respect to basal measurement and suggested that the elevation of blood pressure due to administration of sorafenib can be a marker of VEGF pathway inhibition. Similarly, Rixe, in a series of patients receiving sunitinib for metastatic renal carcinoma, reported that at multivariate analysis grade $\geq$2 hypertension was an independent predictive factor of response (OR = 2.33, $P = 0.009$) and grade 3 hypertension was correlated with a better survival (OR = 5.69, $P = 0.03$) [25].

In contrast with these observations, however, other authors found no correlation between bevacizumab-related hypertension and response or survival. In a retrospective study on 51 patients affected by glioblastoma treated with bevacizumab alone, Wick et al. [26] found no significant difference in response rate and median survival according to hypertension due to the monoclonal antibody. Moreover, Hurwitz analysed the predictive role of hypertension in 5,900 patients treated with bevacizumab and enrolled in AVF2107g [4], NO 16966 [5], AVADO [27], AVAiL [28], RIBBON-1 [29] and AVOREN [30] trials. He found no correlation between blood pressure changes and PFS and OS in 5 of the 6 studies; only in AVF2107g trial, arterial hypertension predicted better PFS and OS in the subgroup of patients with metastatic colorectal cancer treated with chemotherapy plus bevacizumab [31].

These discordant reports might be, at least partially, due to the differences in recording and graduating hypertension. Some authors [10, 24, 25] utilized the NCI-CTC version 2.0, which indicates treatment only for $\geq$G3 hypertension. The frequency of recording blood pressure values (before and after bevacizumab administration, at home between cycles or at hospital visits) is reported only in three studies [10, 24, 26]. Finally, although most authors considered as cut-off G3–G4 hypertension [4, 5, 25, 27, 28], others evaluated the predictive role of any grade [26] or G2–G3 hypertension [24].

The median time of onset of hypertension is not reported in most of the published studies on safety of bevacizumab; however, the incidence of such side effect could depend on the dose of the drug (5 mg/kg/2 weeks versus higher dosage) or on the duration of the period of administration. In the BRiTE register, the incidence of any grade hypertension is 24.6% in patients treated beyond progression versus

19.2% in those treated for first line only [32]. The relationship between the arousal of blood pressure and the dose of bevacizumab is controversial. In metastatic colorectal cancer, 10 mg/kg/2 weeks of bevacizumab were correlated with a higher incidence of any grade hypertension with respect to the half-dose [3]. Similarly, in studies on metastatic NSCLC [28], renal [33] or breast [27] cancer, patients treated with higher-dose bevacizumab had a trend to higher incidence of hypertension (9% vs. 6%; 35.8% vs. 2.7%; 3.2% vs. 0.4%, respectively).

In our study, we adopted the lowest doses of bevacizumab (5 mg/kg/2 weeks or 7.5 mg/kg/3 weeks), the median duration of treatment with bevacizumab was 6.5 months and the hypertension arose quite early (median time of onset = 2.1 months), thus suggesting that the event is not related to the dose or the duration of treatment. We can postulate that the early onset of hypertension is a predictive marker of a tumour-carrier patient sensitive to angiogenic pathway inhibition. In this light, discontinuation of bevacizumab due to the appearance of hypertension should be avoided, and appropriate anti-hypertensive therapy should be administered in order to obtain the best benefit from anti-angiogenic treatment.

In summary, three points should be underlined from this study: hypertension may be considered a common side effect of treatment with bevacizumab and even G2 or superior grade of toxicity may be observed. However, this induced side effect can be easily managed with oral anti-hypertensives such as angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers. Hypertension does not necessitate a dose reduction of bevacizumab because reducing tumour burden remains the top priority and, however, its effect would keep on presenting. Moreover, on the basis of data and results reported in this study, we could hypothesize that bevacizumab-induced arterial hypertension might be considered a positive clinical biomarker predictive of response and of a prolonged survival in patients with metastatic colorectal cancer.

These observations deserve further study in larger population treated with bevacizumab containing regimens, because, if confirmed, they could help in the identification of a useful clinical indicator of the anti-tumour activity of this drug, in predicting a better outcome and, eventually, to identify patients who are more susceptible to this treatment.

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