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Arterial hypertension correlates with clinical outcome in colorectal cancer patients treated with first-line bevacizumab

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Background: Arterial hypertension occurring during antiangiogenic therapy has been correlated with the biological inhibition of the vascular endothelial growth factor-related pathway and may represent a possible clinical marker for treatment efficacy. The aim of our study was to retrospectively assess if grades 2–3 hypertension were associated with response to bevacizumab, progression-free survival (PFS) and survival in metastatic colorectal cancer patients treated with first-line bevacizumab.

Patients and methods: Patients with histologically proven, metastatic colorectal cancer receiving bevacizumab as first-line therapy in combination with irinotecan and 5-fluorouracil were eligible for our analysis.

Results: Thirty-nine metastatic colorectal cancer patients were eligible. Eight patients (20%) developed grades 2–3 hypertension. A partial remission was observed in six of eight cases with bevacizumab-related hypertension (75%) and in 10 of 31 (32%) patients with no hypertension ($P = 0.04$). Median PFS was 14.5 months for patients showing bevacizumab-related hypertension, while it was 3.1 months in those without hypertension ($P = 0.04$). Median overall survival was not reached in patients with hypertension while it was 15.1 months in the remaining cases ($P = 0.11$).

Conclusions: Our data indicate that bevacizumab-induced hypertension may represent an interesting prognostic factor for clinical outcome in advanced colorectal cancer patients receiving first-line bevacizumab.

Key words: arterial hypertension, bevacizumab, colorectal cancer

background

Several growth factor receptor pathways have been implicated in the promotion of tumor angiogenesis. One of the major pathways involved in this process is the vascular endothelial growth factor (VEGF) family of proteins and its receptors, which plays a crucial role in normal and pathologic angiogenesis, resulting in endothelial cell survival, migration and vascular permeability [1].

The VEGF-driven tumor pathway was also demonstrated to represent a novel therapeutic target for an innovative class of antineoplastic agents. Among these antiangiogenetic-targeted treatment modalities, the anti-VEGF mAb bevacizumab has become a new standard of care for first-line treatment of metastatic colorectal cancer, after demonstration of improved response rate and survival in this setting [2, 3].

Subsequently, the expanding role of anti-VEGF treatment for the therapy of metastatic colorectal tumor patients, along with the growing number of cases potentially requiring such a treatment approach, made the need for a correct and reliable identification of responding tumors increasingly crucial.

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However, if on the one hand clinical reports with the use of bevacizumab have shown promising results, on the other hand in these trials no predictive markers of response or resistance were identified. In fact the expressions of VEGF, B-raf, K-ras and other angiogenesis determinant, such as microvessel density, resulted totally inappropriate in patient selection for bevacizumab treatment [3, 4].

Arterial hypertension is a common side-effect during bevacizumab therapy and it is usually easily managed with common medical treatment. In the study by Hurwitz et al., 11% of patients treated with bevacizumab developed grade 3 hypertension versus 2.3% of controls ($P < 0.01$) [4] and a recent meta-analysis showed that severe hypertension requiring multitherapy was noted in 11%–16% of the bevacizumab-treated cohorts [5].

The pathogenesis of VEGF signal inhibition-induced hypertension is still not completely understood. It has been suggested that VEGF may act as a homeostatic factor for blood pressure and that the pharmacological interaction with VEGF or its receptors could result in increased vascular tension, with a consequent raise in blood pressure. Interestingly, Mourad et al. have reported that hypertension could be due to endothelial dysfunction and capillary rarefaction, changes that are both closely associated to bevacizumab treatment [6, 7].

It has also been proposed that VEGF signal antagonism may correlate with the inhibition of nitric synthase and consequently with a decrease in nitric oxide, leading to both vasoconstriction and decreased sodium renal excretion. These latter biological phenomena would ultimately lead to hypertension [5].

The prevalence of hypertension with anti-VEGF and the molecular mechanisms underlying the appearance of antiangiogenic treatment-related hypertension has led Maitland et al. [8] to propose that elevation of blood pressure may act as a biomarker for efficacy of VEGF signal inhibition.

The aim of our study was to retrospectively assess if severe (grades 2–3) hypertension was associated with response to bevacizumab, in a series of metastatic colorectal cancer patients.

We then decided to retrospectively analyze the possible association between bevacizumab-induced hypertension and clinical outcome in terms of response rate, progression free survival (PFS) (primary end points) and survival (secondary end point) in metastatic colorectal cancer patients treated with first-line bevacizumab.

patients and methods

patient selection

Patients with histologically proven, metastatic colorectal cancer receiving bevacizumab as first-line therapy were eligible for our analysis. All patients received bevacizumab at a dose of 5 mg/kg every 2 weeks in association with irinotecan, 5-fluorouracil and folinic acid according to the FOLFIRI regimen. Tumor response was evaluated every 8 weeks by clinicians' assessment and according to the Response Evaluation Criteria for Solid Tumors. Tumor response was evaluated using computed tomography scan or magnetic resonance imaging depending on which imaging methods were used at baseline.

Patients included in this analysis were categorized on the basis of their best tumor response as either responders (patients showing complete or partial response) or nonresponders (patients with stable or progressive disease or whose disease status was not assessable). The sites and date of relapse and the date of death were recorded.

Data regarding blood pressure values were recorded before the infusion of bevacizumab, at half infusion, immediately after and after 1 h from the end of bevacizumab treatment. The highest value of arterial hypertension recorded was decisive for the definition of bevacizumab-induced arterial hypertension. Arterial hypertension was graduated by National Cancer Institute—Common Toxicity Criteria toxicity scale version 2.0. Patients were divided in two groups, as they experimented or not grade 2 or 3 bevacizumab-related arterial hypertension. Grades 2–3 arterial hypertension was chosen as a cut-off level for hypertension definition on the basis of previous reports indicating this level as biologically and clinically relevant [3, 7–9].

data management and statistical analysis

Statistical analysis was carried out with MedCalc package (MedCalc® v9.4.2.0).

The association between categorical variables was estimated by Fisher's exact test. Survival distribution was estimated by the Kaplan–Meier method [10]. Significant differences in probability of relapsing between the strata were evaluated by log-rank test. For statistical analysis, overall survival (OS) and PFS were defined, respectively, as the interval between the start of bevacizumab therapy to death or last follow-up visit and as the interval between the start of bevacizumab therapy to clinical progression or death or last follow-up visit if not progressed.

A significant level of 0.05 was chosen to assess the statistical significance.

results. Thirty-nine metastatic colorectal cancer patients were eligible for our analysis: 30 patients with primary colon tumor (77%) and nine with primary rectal tumor (23%). Twenty-five patients were males (64%) and 14 females (36%); median age at diagnosis was 58 years (range 30–70). Sites of metastasis were liver in 32 patients, lung in eight, peritoneum in five, distant lymph nodes in 10 and bones in two.

Sixteen patients (41%) were responders while 23 were nonresponders with no complete remissions observed in our series. For the entire study population, median PFS was 4.1 months, while median OS was not reached. Eleven patients (35.5%) presented a medical history of arterial hypertension under control with medical treatment. In all cases, blood pressure at baseline was within normal range.

In the whole study population, eight patients (20%) developed grades 2–3 bevacizumab-related hypertension. Patient's characteristics resulted statistically comparable among patients with or without hypertension (Table 1). Only the male/female ratio seemed to differ between the two groups of patients analyzed, with an apparent greater proportion of males in the group of patients without bevacizumab-related arterial hypertension. However, this difference was not statistically significant.

A partial remission was observed in six of eight cases with bevacizumab-related hypertension (75%) and in 10 of 31 (32%) patients with no hypertension (P 0.04).

Median PFS was 14.5 months for patients showing bevacizumab-related hypertension, while it was 3.1 months in those who did not develop hypertension during the course of bevacizumab treatment ($P = 0.04$) (Figure 1). Median OS for patients with or without bevacizumab-related hypertension was not statistically different (Table 1).

conclusions

Biological agents for the treatment of metastatic colorectal cancer have been promoted as 'targeted therapy' because they were molecularly designed to affect tumor growth by targeting specifically tumor-activated biological pathway, hopefully with an improved antitumoral efficacy but without causing the usual toxicity profile of common chemotherapy agents such as myelosuppression and nausea [11].

However, the appearance of new, usually nonsevere, but clinically meaningful chronic toxic effects, like skin rash (anti-EGFR linked) and vascular injuries (anti-VEGFR linked) as well as the exponential increase of the economic treatment costs, urged the need for reliable predictive factors able to identify patients (or tumors) more likely to benefit from such a treatment approach [2]. Arterial hypertension occurring during antiangiogenic therapy (such as bevacizumab) has been correlated with the biological inhibition of the VEGF-related pathway and given its molecular link with antiangiogenic mechanisms may represent a possible clinical marker for treatment efficacy, analogously to what has been demonstrated for skin rash and cetuximab [12]. In our study, eight patients developed grades 2–3 hypertension (20%) which is similar to what has been observed in clinical trials investigating the use of bevacizumab in metastatic colorectal patients [3]. The two groups of patients (those with and without bevacizumab-related hypertension) resulted comparable for all clinical characteristics examined. The apparent greater proportion of males among patients without

Table 1. Patients' characteristics

	Patients with bevacizumab-related hypertension	Patients without bevacizumab-related hypertension	*P*
M/F	3/5	22/9	
Age at diagnosis (range)	53 years (48–70)	58 years (30-69)	
Primary tumor (colon/rectum)	6/2	24/7	
ECOG PS 0–1	5 (62.5%)	20 (64.5%)	
ECOG PS 2–3	3 (37.5%)	11 (35.5%)	
Medical history of arterial hypertension	2 (25%)	9 (29%)	
Antihypertensive treatment			
Diuretics/beta-adrenoceptor blocking drugs	5 (50%)	5 (55%)	
ACE inhibitors	4 (40%)	3 (33%)	
Others	1 (10%)	1 (12%)	
Previous adjuvant chemotherapy	3 (37.5%)	13 (42%)	
Primary tumor (colon/rectum)	6/2	24/7	
Sites of metastasis (%)			
Liver	6 (43%)	26 (60%)	
Lung	2 (14%)	6 (14%)	
Peritoneum	1 (7%)	4 (9%)	
Distant lymph nodes	4 (29%)	6 (14%)	
Bone	1 (7%)	1 (2%)	
Baseline CEA			
>30 ng/ml	2 (25%)	10 (32%)	
<30	5 (63%)	18 (58%)	
Not done	1 (12%)	3 (10%)	
Median duration of treatment (weeks)	56.4	12.2	
Dose administered (percentage of the planned dose)			
Irinotecan/5-FU bolus/infusional 5-FU	75/90/90	80/90/90	
Bevacizumab	100	100	
Second-line chemotherapy (*n*)	6 (75%)	28 (90%)	
Oxaliplatin based	5 (83%)	24 (86%)	
Others	1 (17%)	4 (14%)	
Response rate (%)	6/8 (75%)	10/31 (32%)	0.04
Median PFS (months)	14.5	3.1	0.04
Median OS (months)	Not reached	15.1	

Only statistically significant *P* values have been indicated.
ECOG PS, Eastern Cooperative Oncology Group performance status; CEA, carcinoembryonic antigen; 5-FU, 5-fluorouracil; PFS, progression-free survival; OS, overall survival.

bevacizumab-related arterial hypertension (although not statistically significant) does not seem to have an univocal, clear explanation. Since males are more frequently affected by primary hypertension (the commonest form of arterial hypertension), one would have expected a higher rate of bevacizumab-related hypertension in this group. We can then speculate that bevacizumab-related hypertension may involve different biological pathways in comparison with other forms of hypertension. It is also important to note that this difference may also be due to chance given the small sample size studied. Interestingly, among patients with bevacizumab-related hypertension, we observed a significant improvement in global clinical outcome, particularly in response rate and PFS (response rate 75% versus 32% $P = 0.04$, PFS 14.5 months versus 3.1 months $P = 0.04$). No statistically significant difference was noted in our series for median OS. This may indicate either that the sample size was too small to statistically detect an improved survival or that subsequent lines of treatment made differences in OS difficult to emerge.

Our results seem also to go along with those regarding pancreatic cancer patients treated with gemcitabine and bevacizumab. Nevertheless in these patients early hypertension defined as >grade 2 correlated with response rate, but not with PFS or OS [9].

These observations, if confirmed in larger series of bevacizumab-treated colorectal cancer patients, seem to imply that the identification of a reliable clinical factor such as grades 2–3 arterial hypertension developing during bevacizumab therapy may constitute an early indicator of antitumor activity, whereas lack of this side-effect could instead represent an important warning of lack of activity and maybe ultimately suggest an early change in the treatment strategy [9, 11, 13].

Our data seem also to confirm findings from preclinical and clinical studies suggesting that during an anti-VEGF treatment the inhibition of similar molecular mechanism maybe

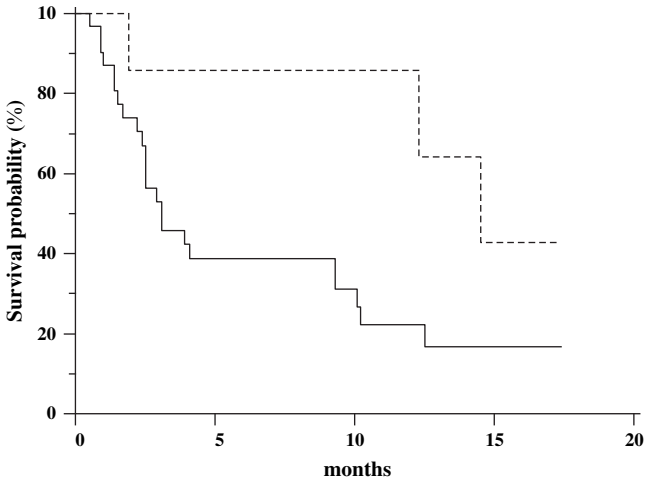

Figure 1. Median progression-free survival of colorectal cancer patients with grades 2–3 bevacizumab-related arterial hypertension (-------) and without bevacizumab-related arterial hypertension (———) ($P = 0.04$).

responsible for both an elevated blood pressure and clinical outcome.

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