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Predictive Potential of Angiogenic Growth Factors and Circulating Endothelial Cells in Breast Cancer Patients Receiving Metronomic Chemotherapy Plus Bevacizumab

Angelica Calleri,[1] Anna Bono,[1] Vincenzo Bagnardi,[4] Jessica Quarna,[1] Patrizia Mancuso,[1] Cristina Rabascio,[1] Silvia Dellapasqua,[2,3] Elisabetta Campagnoli,[2,3] Yuval Shaked,[5] Aron Goldhirsch,[3] Marco Colleoni,[2,3] and Francesco Bertolini[1]

Abstract

Purpose: The association of chemotherapy and antiangiogenic drugs has shown efficacy in clinical oncology. However, there is a need for biomarkers that allow selection of patients who are likely to benefit from such treatment and are useful for indicating best drug combination and schedule.

Experimental Design: We investigated the predictive potential of six angiogenic molecules/transcripts and nine subpopulations of circulating endothelial cells (CEC) and progenitors (CEP) in 46 patients with advanced breast cancer treated with metronomic cyclophosphamide and capecitabine plus bevacizumab.

Results: Median time to progression was 281 days. Baseline CECs higher than the first quartile were associated with an increased time to progression ($P = 0.021$). At progression, CECs were markedly reduced ($P = 0.0002$). In the cohort of 15 long-term responders, who progressed later than 1 year after beginning of therapy, circulating vascular endothelial growth factor (VEGF)-A levels measured after 2 months of therapy were significantly reduced, and there were significant trends toward lower levels of PDGF-BB, CEPs, and CECs. At the time of progression, angiogenic growth factors VEGF-A and basic fibroblast growth factor were significantly increased.

Conclusions: Baseline CECs (likely reflecting an active vascular turnover) predicted a prolonged clinical benefit. At the time of relapse, a pattern of decreased CECs and increased angiogenic growth factors suggested a switch toward a different type of cancer vascularization. VEGF-A and basic fibroblast growth factor levels after 2 months of therapy were also useful to identify patients whose disease was likely to progress. These biomarkers are likely to be useful for treatment selection and might be incorporated in design of future studies. (Clin Cancer Res 2009;15(24):7652–7)

Authors' Affiliations: [1]Laboratory of Hematology-Oncology, [2]Medical Senology Research Unit and [3]Division of Medical Oncology, Departments of Pathology and Medicine, European Institute of Oncology; [4]Division of Epidemiology and Biostatistics, European Institute of Oncology, and Department of Statistics, University of Milan-Bicocca, Milan, Italy; and [5]Department of Molecular Pharmacology, Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

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Note: A. Calleri and A. Bono contributed equally to this work.

Requests for reprints: Francesco Bertolini, Laboratory of Hematology-Oncology, European Institute of Oncology, via Ripamonti 435, 20141 Milan, Italy. Phone: 39-02-57489535; Fax: 39-02-57489537; E-mail: francesco.bertolini@ieo.it.

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The addition of the anti–vascular endothelial growth factor (VEGF)-A antibody bevacizumab to regular dose chemotherapy has led to an improvement in progression-free survival in patients suffering from advanced breast cancer. However, this improvement has been thus far limited to a few months, and at a cost of significant toxicity. The synergistic mechanism between chemotherapy and bevacizumab is currently unclear (1). Furthermore, it is not fully understood whether the benefit from the combination is similar for all patients or greater in some patients and reduced (or absent) in others. Thus, there is a compelling need for biomarkers useful for distinguishing between patients who are likely to benefit from the combination therapy from those for whom the balance between the benefit and the side effects is less convenient (1–5).

We have recently reported the results of a phase II clinical study with combined metronomic chemotherapy (a continuous, daily administration of low-dose cytotoxic drugs with no treatment-free gaps, see refs. 6–11) and bevacizumab. This combination was particularly effective and safe in advanced breast cancer (12). Among the 46 patients who received daily oral cyclophosphamide and capecitabine plus i.v. bevacizumab

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Translational Relevance

Antiangiogenic drugs are increasingly used by clinical oncologists, but little is known about their mechanism of action, alone or in combination with cytotoxic drugs. Moreover, there is an urgent need for biomarkers able to predict the response to antiangiogenic therapies and to define the optimal biological dose/schedule of these drugs. We have recently reported that the association of metronomic chemotherapy and bevacizumab was effective in advanced breast cancer patients. In these patients, an active vascular turnover suggested by high levels of circulating endothelial cells predicted a prolonged clinical benefit, and decreased circulating endothelial cells and increased angiogenic growth factors observed at relapse suggested a switch toward a different type of cancer vascularisation. The measurement of vascular endothelial growth factor A and basic fibroblast growth factor after 2 months of therapy were also useful to identify patients who were likely to progress. These biomarkers look promising for treatment selection, patient monitoring during therapy, and for study design.

every 2 weeks, the overall response rate was 48% and the clinical benefit (including complete and partial responses plus prolonged stable disease) was 68%.

Here, we report on long-term patterns of angiogenic growth factors and circulating endothelial cells (CEC) in these patients. Some of these markers were hypothesized to have a predictive clinical potential that might be useful in future clinical studies. The most interesting observation was done assessing a cohort of 15 patients who were treated with the combination for >1 year. To our knowledge, there are no clinical reports on the use of bevacizumab and metronomic chemotherapy for such a prolonged period.

Patients and Methods

Patients. Details about the clinical study (conducted at the European Institute of Oncology, Milan, Italy) have been described by Dellapasqua et al. (12). In brief, patients ages 18 to 80 y with histologically proven advanced breast cancer received 10 mg/kg bevacizumab (Avastin, Roche) i.v. every 14 d in combination with cyclophosphamide (Endoxan, Baxter), one 50-mg tablet daily at 9 a.m., plus capecitabine (Xeloda, Roche), one 500-mg tablet thrice daily after meals. Cycles were repeated every 14 d. The trial was approved by the local Ethical Committee. Written informed consent was required.

Response to treatment was evaluated every four treatment cycles using Response Evaluation Criteria in Solid Tumors (13).

Biomarker evaluations. CEC and circulating endothelial progenitors (CEP) and the circulating levels of VEGF-A, basic fibroblast growth factor (b-FGF), PDGF-BB, SDF-1α as well as the copies of mRNA coding for *VE-Cadherin*, *VEGFR1*,*VEGFR2*, *VEGFR3*, *PDGFR-β*, and *CD133* genes were measured on day 0 (before the beginning of therapy), 14, 56, and on the day of clinical progression.

In brief, CECs and CEPs were measured by six-color flow cytometry as previously described (14, 15). CECs were enumerated as DNA+, CD45-, and CD31+CD146+ cells. Viable and apoptotic CECs, and CEC subpopulations expressing VEGFR1, VEGFR2, or VEGFR3 were also enumerated. The endothelial nature of CECs was confirmed by the finding of Weibel-Palade bodies and high levels of the endothelial-specific gene *VE-Cadherin* in purified CECs (15). CEPs were enumerated as DNA+, CD45-, CD133+CD34+ cells or as DNA+, CD45-CD34+ cells (14, 15).

Plasma levels of VEGF-A, b-FGF, PDGF-BB, and SDF-1α were measured by ELISA according to manufacturer's instructions (R&D Systems). Copies of mRNA coding for *VE-Cadherin*, *VEGFR1*, *VEGFR2*,

Table 1. Patients' characteristics at baseline

Characteristic	No. of patients	%
No. of enrolled	47	
No. of assessable	46	
Age, y		
Median	57.5	
Range	35-75	
Body weight, kg		
Median	65	
Range	45-99	
Menopausal status		
Premenopausal	15	33
Postmenopausal	31	67
Metastatic sites*		
Bone	16	35
Lung	14	30
Liver	21	46
Lymph nodes	19	41
Pleura	7	15
Others	6	13
No. of metastatic sites		
1	20	43
2	19	41
≥3	7	15
Tumor hormone receptor status†		
ER positive and PgR positive	15	33
ER positive and PgR negative	20	43
ER negative and PgR negative	11	24
HER2/neu status		
Absent	17	37
1+	22	48
2+	6	13
3+	1	2
Prior neoadjuvant therapy		
No	35	76
CT	6	13
CT/HT	5	11
Prior adjuvant therapy		
No	11	24
CT	6	13
HT	10	22
CT/HT	19	41
Prior therapy for metastatic disease		
No	11	24
CT	3	7
HT	16	35
CT/HT	14	30
CT/HT/trastuzumab	2	4
No. of prior metastatic CT regimens		
0	27	59
1	11	24
≥2	8	17
Prior anthracycline	29	63
Prior taxane	11	24

Abbreviations: ER, estrogen receptor; PgR, progesterone receptor; CT, chemotherapy; HT, hormone therapy.
*Multiple sites possible.
†Positive: ≥ 10%.

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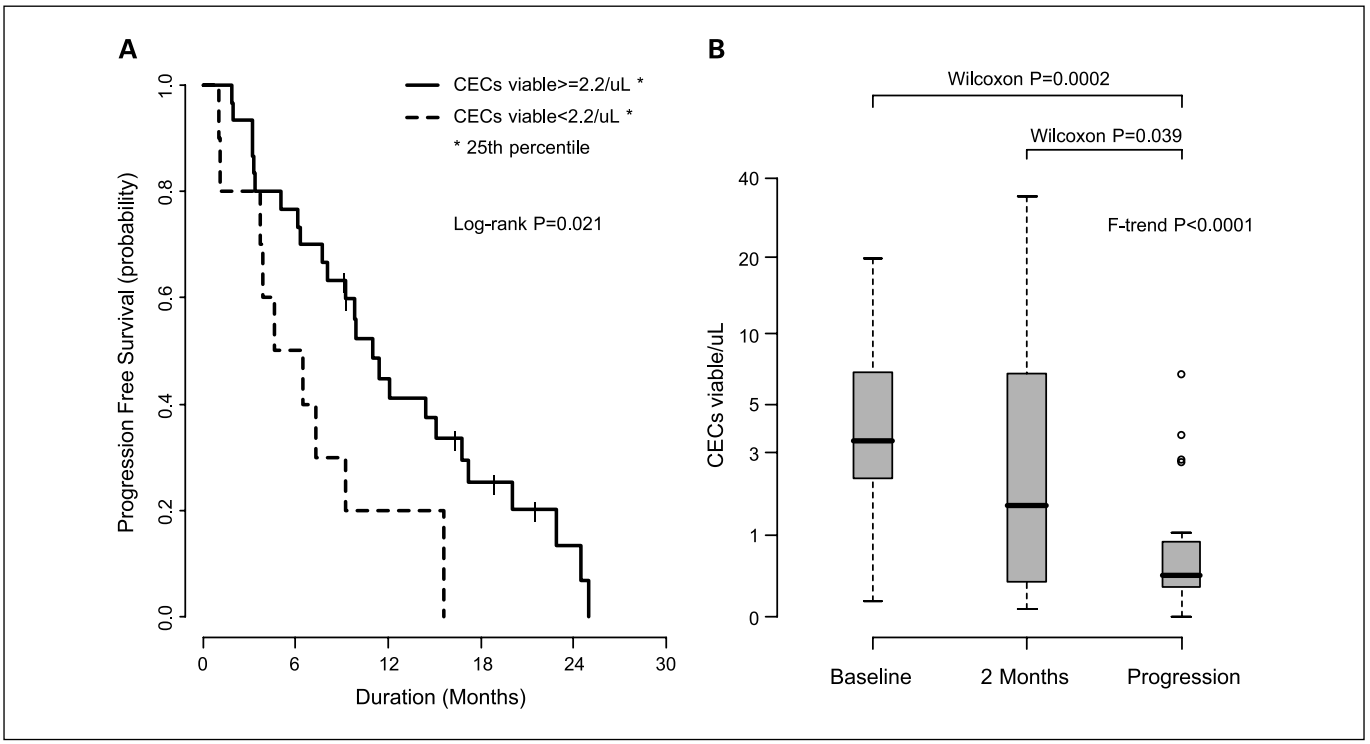

Fig. 1. *A,* PFS according to CECs at baseline. Censoring is indicated by tick marks. *B,* CECs at baseline, 2 mo after beginning of therapy and progression. Boxes, the interquartile range; lines, location of first quartile, median, and third quartile. Whiskers (standard span) were extended to 1.5× the interquartile range. ○, outliers beyond the standard span.

VEGFR3, *PDGFR-β*, and *CD133* genes were measured following a protocol previously described by Rabascio et al. (16).

Statistical analysis. To evaluate differences in the distribution of the markers between pairwise time points, overall and according to long-term responsiveness, the Wilcoxon signed-rank test and the Wilcoxon rank-sum test were used, respectively. Linear regression models for repeated measures were used to assess temporal trends of each marker for the whole group of patients. Time to progression (TTP) was defined as the length of time from the start of treatment to disease progression. TTP was censored at the date of last visit for patient still treated or at the time of discontinuation for patients suspending bevacizumab before progressive disease. The progression-free survival (PFS) was estimated using the Kaplan-Meier method.

The log-rank test was used to test differences in PFS between subgroup of patients: cut off values for each marker were set at the 25th, 50th, or 75th percentile. Analysis of markers evaluated at 2 mo from the start of treatment was based on the landmark approach (17), excluding patients going off protocol before month 2. Cox proportional hazard model with restricted cubic splines was used to investigate the shape of the relationship between each marker and the hazard of progression (18).

Due to the skewness of the distribution of the considered markers, the log-transformed data were used in the analyses and reported on the log scale in the figures.

All analyses were carried out with the SAS software (SAS Institute) and the R[6] software with the Harrell's Design and Hmisc libraries.

All reported *P* values were two sided.

Results

Among the 46 evaluated patients, 3 patients discontinued bevacizumab for personal or clinical reasons before progressive disease, and were not considered in the analysis for long-term response. Two patients were still treated with the combination at the time of the analysis. Median TTP was 281 days (95% confidence interval, 195-452). The full discussion of the clinical long-term results are beyond the scope of this article, which focuses on the prognostic potential of the markers investigated in the study, and are discussed in a separate article.[7]

Patients' characteristics are described in Table 1. A previous therapy (including chemotherapy, hormonal therapy, or anti-HER2 therapy) was administered to 11 of 15 (73%) of long-term responders versus 21 of 28 (75%) of early failure patients ($P = 1.0$). Previous chemotherapy was administered to 4 of 15 (27%) of long-term responders versus 13 of 28 (46%) of early failures patients ($P = 0.32$).

Investigating six angiogenesis-related molecules and different subpopulations of CECs and CEPs, we found that baseline CEC values higher than the first distribution quartile were significantly associated with an increased TTP ($P = 0.021$; Fig. 1A). The prognostic potential of viable and apoptotic CECs was similar (data not shown). At the time of progression, the number of CECs (either viable and apoptotic) was markedly reduced when compared with previous values ($P = 0.0002$; Fig. 1B).

The VEGF ELISA assay used in this study measured bevacizumab-bound as well as bevacizumab-unbound VEGF. Serial dilution studies indicated that in EDTA plasma samples the minimum detectable VEGF dose was <5 pg/mL. Intra-assay and interassay

[6] http://cran.r-project.org/

[7] Campagnoli et al., submitted.

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precision tests indicated that in our VEGF evaluations, the coefficient of variation was always lower than 7%. In the cohort of 15 long-term responders (defined as patients who progressed later than 1 year after the beginning of the therapy), circulating VEGF-A levels measured after 2 months of therapy were significantly reduced compared with the remaining patients ($P = 0.01$; Fig. 2D). In fact, low VEGF-A levels after 2 months of therapy were associated with a significantly improved TTP ($P = 0.0052$; Fig. 2A). Similarly, b-FGF values found to be below the third quartile after 2 months of therapy were associated with a significantly improved TTP ($P = 0.029$; Fig. 3A).

At the time of progression, we observed a significant increase of the circulating levels of angiogenic growth factors VEGF-A ($P = 0.023$; Fig. 2C) and b-FGF ($P = 0.038$; Fig. 3B). Also, in long-term responders evaluated after 2 months of therapy, there was a significant trend toward lower levels of VEGF-A and PDGF-BB ($P < 0.0001$ and 0.01, respectively), CD133+ CEPs ($P = 0.01$), total CECs, as well as VEGFR1+ and VEGFR2+ CECs ($P < 0.001$). Since many markers and cut off values were evaluated in these analyses and since reported P values have not been adjusted for multiple comparisons in this very large explorative investigation, statistical significance should be interpreted with caution.

Discussion

The long-term evaluation of this group of advanced breast cancer patients treated with metronomic chemotherapy plus bevacizumab confirmed the efficacy of this therapeutic approach (12), which was associated with an overall response rate of 48% (95% confidence interval, 33-63%), an overall clinical

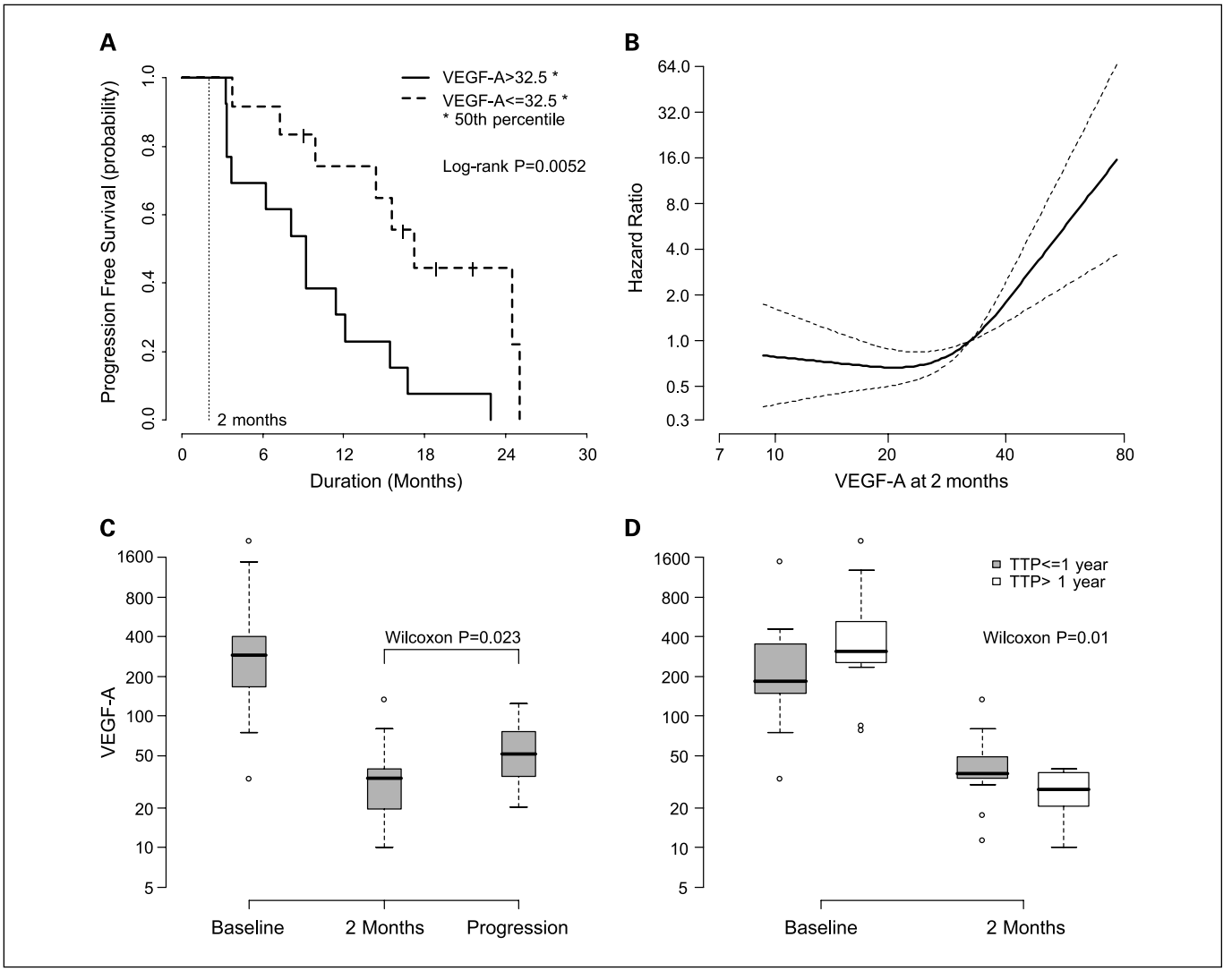

Fig. 2. *A,* PFS (2-mo landmark) according to VEGF-A circulating levels at 2 mo after beginning of therapy. Censoring is indicated by tick marks. *B,* relationship between the VEGF-A circulating levels at 2 mo and hazard of progression (2-mo landmark). Solid line, the hazard ratio, using as reference the VEGF-A median level; dotted lines, the hazard ratio 95% confidence bands. *C,* VEGF-A circulating levels at baseline, 2 mo after beginning of therapy and progression. Boxes, the interquartile range; lines, indicate location of first quartile, median, and third quartile. Whiskers (standard span) were extended to 1.5× the interquartile range. ○, outliers beyond the standard span. *D,* VEGF-A circulating levels at baseline and 2 mo after beginning of therapy, according to TTP. Boxes, the interquartile range; lines, location of first quartile, median, and third quartile. Whiskers (standard span) were extended to 1.5× the interquartile range. ○, outliers beyond the standard span.

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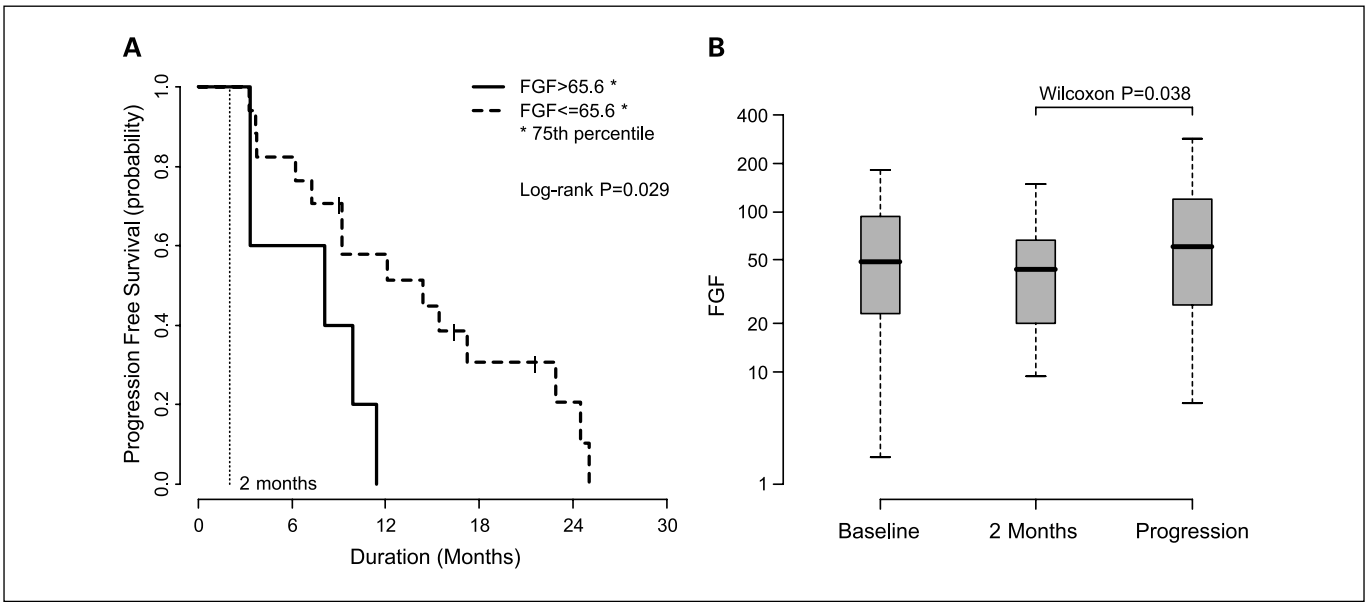

Fig. 3. *A,* PFS according to FGF circulating levels at baseline. Censoring is indicated by tick marks. *B,* FGF circulating levels at baseline, 2 mo after beginning of therapy and progression. Boxes, the interquartile range; lines, location of first quartile, median, and third quartile. Whiskers (standard span) were extended to 1.5× the interquartile range.

benefit (including stable disease of ≥24 weeks) of 68% (95% confidence interval 51-81%), and can be safely administered for well more than 1 year.

The analysis of the biomarkers measured throughout the study indicated that the baseline number of CECs is a strong predictive marker for clinical response and benefit. CECs are currently thought to represent an indirect marker of vascular remodeling and turnover (14), and a recent validation article has confirmed the endothelial nature of CECs measured and sorted by flow cytometry (15). Our findings suggest that patients with higher CEC counts, reflecting according to animal models an active vascular remodeling in cancer vessels (19), are most likely to benefit from the association of metronomic chemotherapy plus bevacizumab.

The finding that CECs were markedly reduced at the time of progression has several possible explanations, including a lack of relationship between CEC count and cancer progression. However, the statistically significant decrease in CEC count at the time of relapse might suggest that escape from this type of therapy implies a (possibly radical) switch toward a different vascularization of the neoplastic lesions. More studies in preclinical models are needed and are currently ongoing to understand whether such switch is toward the cooption of (more stable) vessels from the non-neoplastic tissue, a compensatory pathway of angiogenesis that may be VEGF independent, or toward a new type of neoangiogenesis involving different vessels, more stable and with lower turnover (20–22). It must be noted that at the time of progression two angiogenic growth factors, namely VEGF-A and b-FGF, were significantly increased when compared with previous values. This finding also suggests a distinct angiogenic switch associated with escape from therapeutic effects of the combination.

The measurement of circulating levels of VEGF-A indicated that in long-term responders, after 2 months of therapy, this angiogenic growth factor was markedly reduced when compared with other patients. As shown in Fig. 2B, the relationship between the circulating levels of VEGF-A after 2 months of therapy and risk of progression was not linear (P for nonlinearity < 0.01). Taking as reference the median value, the estimated log hazard of progression remained stable for values below the reference and increased dramatically for values above. This novel observation sheds light on a previously unrecognized clinical relevance of the measurement of VEGF-A in patients receiving metronomic chemotherapy plus the anti–VEGF-A antibody bevacizumab. The measure of this angiogenic growth factor did not seem to have a predictive potential, but VEGF-A values after the first 2 months of therapy could serve as a surrogate marker to identify patients who are less likely to have a prolonged benefit from the therapy and might thus be considered for a different modulation of antiangiogenesis (e.g., an increase in bevacizumab dosage or its use with a different combination of drugs).

These data indicate that patients with active vascular turnover, as suggested by high levels of CECs, seem to obtain a larger clinical benefit from the combination of metronomic chemotherapy and bevacizumab. At the time of relapse, a pattern of decreased CECs and increased angiogenic growth factors suggests a switch toward a different type of cancer vascularisation. Also, VEGF-A and b-FGF levels after 2 months of therapy seem to have clinical relevance for identifying patients likely to have progressive disease. Although our results must now be confirmed in larger prospective clinical trials, these patterns might be used to design future clinical studies and to better understand mechanisms of escape from therapies involving antiangiogenic drugs (21–24).

Another interesting potential predictor of response to bevacizumab-containing metronomic therapy was recently described

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by Lenz et al. (25). These authors investigated a number of single nucleotide polymorphisms and found that an *IL-8* gene single nucleotide polymorphism was associated with clinical response in ovarian cancer patients treated with metronomic chemotherapy plus bevacizumab. More studies are now needed to compare the predictive and prognostic potential of single nucleotide polymorphisms versus the markers investigated in the present study.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

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