between cisplatin and carboplatin. All the reported cases with such an allergy had previously tolerated their platinum-based treatments. Prophylactic treatment with antihistamines and corticosteroids failed to prevent recurrent anaphylactic reactions to cisplatin [5].

Activity of oxaliplatin in colorectal cancer is now well established, but with the increasing use of this drug, prescribers must be aware of possible sudden and severe anaphylactic reactions.

1. Becouarn Y, Ychou M, Ducreux M, *et al.* Oxaliplatin (L-OHP) as first-line chemotherapy in metastatic colorectal cancer (MCRC) patients: preliminary activity/toxicity report. *Proc ASCO* 1997, **16**, 804.
2. De Gramont A, Vignoud J, Tournigand C, *et al.* Oxaliplatin with high dose leucovorin and 5-fluorouracil 48-hour continuous infusion in pretreated metastatic colorectal cancer. *Eur J Cancer* 1997, **33**(2), 214–219.
3. Lévi F, Zidani R, Misset JL. Randomised multicentre trial of chronotherapy with oxaliplatin, fluorouracil, and folinic acid in metastatic colorectal cancer. *Lancet* 1997, **350**, 681–686.
4. Von Hoff DD, Slavik M, Muggia FM. Allergic reactions to cis platinum. *Lancet* 1976, **i**, 90.
5. Goldberg A, Altares M, Mekori Y, *et al.* Anaphylaxis to cisplatin: diagnosis and the value of pretreatment in prevention of recurrent allergic reactions. *Ann Allergy* 1994, **73**, 271–272.

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Vascular Endothelial Cell Growth Factor (VEGF) Serum Concentrations Change According to the Phase of the Menstrual Cycle

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ANGIOGENESIS IS a highly restricted process in adults. In women, new vessel development only takes place in wound healing, pregnancy and during the menstrual cycle. In the proliferative phase, microvessels are formed in the growing endometrium and in the differentiating follicle. In the secretory phase, capillaries penetrate into the granulosa layer of the corpus luteum [1]. Given the strong association of fast tumour growth and elevated serum levels of basic fibroblast growth factor (bFGF) and of vascular endothelial cell growth factor (VEGF) [2, 3], we investigated whether physiological angiogenesis also affects serum concentrations of these factors.

6 healthy premenopausal women, not using oral contraceptives or other drugs, agreed to participate and had a blood sample taken at the start of their menstrual cycle (early proliferative phase), at the time of expected ovulation and during the secretory phase of the cycle, for two cycles. The distribution of time points is given in Table 1. If possible, a morning and an afternoon sample were taken, resulting in six samples per menstrual cycle per woman. Serum was immediately separated and stored at $-80°C$. VEGF and bFGF concentrations were determined by enzyme-linked immunosorbent assay (ELISA) (R&D Systems Europe, Oxford, U.K.). Oestradiol, progesterone, follicle-stimulating hormone (FSH) and luteinising hormone (LH) concentrations were determined by microparticle enzyme immunoassay (Abbott, Chicago, Illinois, U.S.A.).

Only data for women who supplied blood samples at the three phases of their menstrual cycle(s) were considered in this analysis (45 samples of nine menstrual cycles). The median length of the menstrual cycle was 25 days (mean 26.3; range 21–32 days). Oestradiol and LH levels per cycle increased by 1.73-fold (median; 5-fold mean) and 2.17-fold (median; 2.18-fold mean), respectively, from the peri-ovulatory to the early proliferative phase. Progesterone levels increased by 16-fold (median; 23-fold mean) the secretory phase from the peri-ovulatory phase. The median bFGF serum concentration of all samples was 1.6 pg/ml (mean 3.2 ± 4.8 (standard deviation); range 0.4–30.6). The median VEGF serum concentration was 153 pg/ml (mean 173 ± 95; range 30–403). Ninety-five per cent of all bFGF serum concentrations were lower than 12 pg/ml. For VEGF, the 95th percentile value was 400 pg/ml. The accordance rates of morning and afternoon bFGF and VEGF serum concentrations according to the respective median values were 58 and 89%, respectively.

When median bFGF and VEGF serum concentrations were calculated per cycle, a significantly lower proportion had VEGF serum levels above the median in the peri-ovulatory phase (3/14, 21%) as compared with the early proliferative (13/15, 87%) and secretory phases (9/16, 56%) (Table 1). A

Table 1. *Basic fibroblast growth factor (bFGF) and vascular endothelial cell growth factor (VEGF) serum concentrations in three phases of the menstrual cycle*

	Phase of menstrual cycle		
	Early proliferative ($n=15$)	Peri-ovulatory ($n=14$)	Secretory ($n=16$)
Day (median (mean; range))	2 (3.0; 1–9)	12 (12.4; 10–18)	21 (21.9; 18–31)
Number of samples above cycle-specific median concentration ($n=45$)			
bFGF	8 (53%)	7 (50%)	9 (56%)
VEGF*	13 (87%)†	3 (21%)§	9 (56%)

Comparison of fractions: *2×3 multiple test with 2 degrees of freedom: $\chi^2=12.49$, $P=0.0019$, †Early proliferative phase versus peri-ovulatory phase: $\chi^2=12.46$, $P=0.0004$. Early proliferative phase versus secretory phase: $\chi^3=3.48$, $P=0.06$. §Peri-ovulatory phase versus secretory phase: $\chi^2=3.77$, $P=0.05$.

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trend towards a higher proportion with elevated VEGF serum levels in the early proliferative versus secretory phase was also observed. For bFGF no differences were observed.

These data suggest that the amount of circulating VEGF in healthy premenopausal women fluctuates in accordance with processes of physiological angiogenesis related to the menstrual cycle. Together with our data of cancer patients [2, 3], this also suggests that paracrine-acting angiogenic factors might have an endocrine effect, which is compatible with the tumour growth enhancement by wound healing at a distance observed in animals [4]. If circulating VEGF is active, any surgical intervention in cancer patients causing shedding of cells in the blood stream might increase the risk of distant metastases at a moment of elevated VEGF. To test the above-mentioned hypothesis, we suggest that angiogenic factor levels should be determined in studies analysing the effect of timing of surgery on prognosis in breast cancer patients.

1. Findlay JK. Angiogenesis in reproductive tissues. *J Endocr* 1986, **111**, 357–366.
2. Dirix LY, Vermeulen PB, Hubens G, *et al.* Serum basic fibroblast growth factor and vascular endothelial growth factor and tumour growth kinetics in advanced colorectal cancer. *Ann Oncol* 1996, **7**, 843–848.
3. Dirix LY, Vermeulen PB, Pawinski A, *et al.* Elevated levels of the angiogenic cytokines basic fibroblast growth factor and vascular endothelial growth factor in sera of cancer patients. *Br J Cancer* 1997, **76**, 238–243.
4. Bogden AE, Moreau J-P, Eden PA. Proliferative response of human and animal tumours to surgical wounding of normal tissues: onset, duration and inhibition. *Br J Cancer* 1997, **75**, 1021–1027.