xenograft of soft tissue sarcoma growing in nude mice [5]. It has a documented activity in relatively chemoresistant diseases, such as cancer of the pancreas [1, 2], and a palliative role in other malignancies [6]. Finally, it was the hopeless prognosis of our young patient with relapsing osteosarcoma while under chemotherapy that led us to the enthusiastic application of one of the available new and unexplored agents [4]. Our experience in this unique case of osteosarcoma points to several facts. Gemcitabine was found to be effective in achieving stabilisation and even a minimal response of an osteosarcoma refractory to standard chemotherapy consisting of doxorubicin, high-dose methotrexate, cisplatin and ifosfamide. Although disease stabilisation is generally accepted as failure of chemotherapy, in this rare case it should be regarded as success in view of the failure of other drugs, Gemcitabine administration also resulted in a clear clinical benefit response, manifested by improvement of quality of life, reduction of narcotic consumption, restoration of mobility, improvement of the Karnofsky performance status, and recovery from previous alopecia. The toxicity profile was low and included mild myelotoxicity, limb oedema and rash. It is clear that no treatment recommendations can be made on the basis of a single case report. However, it may be warranted to investigate the activity of gemcitabine in other patients with refractory osteosarcoma.

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European Journal of Cancer, Vol. 34, No. 8, pp. 1297–1298, 1998

Printed in Great Britain
0959-8049/98 $19.00+0.00

PII: S0959-8049(98)00064-1

Severe Anaphylactic Reactions to Oxaliplatin

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OXALIPLATIN (L-OHP, *trans*-L-1,2-diaminocyclohexane oxaliplatinum), is a new platinum compound which has shown *in vitro* and *in vivo* antitumoral activity in colorectal cancer. Oxaliplatin has been largely studied in patients with metastatic colorectal cancer. Administered as a single agent, the response rate according to WHO criteria is 10% in patients resistant to 5-fluorouracil (5-FU) and 27% in previously untreated patients [1]. A synergy with 5-FU has also been demonstrated, with constant-rate or chronomodulated infusions [2, 3]. The toxicity profile of oxaliplatin is different from cisplatin: there is no renal or auditory toxicity and the main dose-limiting toxic effect is a cumulative sensitive peripheral neuropathy. Other toxic effects include mild myelosuppression [1, 2].

We report that anaphylactic reactions to oxaliplatin can occur and be life threatening. The first case occurred in a 59 year old man treated for metastatic colon adenocarcinoma. After failure of a 5-FU–leucovorin combination after five cycles, he was included in a phase II study with high-dose leucovorin and 5-FU in continuous infusion combined with oxaliplatin (100 mg/m^2) every 2 weeks. Six cycles passed uneventfully. Immediately after the beginning of the seventh cycle 2-h infusion of oxaliplatin, the patient complained of a burning sensation of the neck and the face with a flush, shortness of breath, sweating and dizziness. Oxaliplatin was immediately discontinued. Clinical examination revealed a reduced systolic blood pressure (SBP < 50 mm Hg) and urine loss. He was consequently treated with intravenous dexamethasone, epinephrine, macromolecules and nasal oxygen. He fully recovered 9 h after the accident. Two weeks later, the same regimen was reintroduced with a longer perfusion time of oxaliplatin. As soon as the drug was delivered, the patient developed the same symptoms. The drug was definitively withdrawn.

Currently, we have observed four additional cases with the same severe anaphylactic reaction (see Table 1). The estimated frequency is 2%.

Anaphylactic reactions to cisplatin have already been described. The reactions consist of facial oedema, wheezing, tachycardia and hypotension within a few minutes of intravenous administration [4]. Carboplatin has also been shown to be responsible for allergic reactions. Based on skin test reactivity, it has been shown that there is a cross-reactivity

Table 1. *Five cases of anaphylactic reactions to oxaliplatin*

Age	Sex	Cycle	Oxaliplatin dose (mg/m^2)	Symptoms
59	M	7	100	Reduced SBP, flushing, sweating, dizziness, burning sensation
77	M	8	100	Reduced SBP, flushing, sweating, mouth pricking sensations. Same symptoms at reintroduction
64	F	5	85	Reduced SBP, flushing, sweating
75	F	8	85	Reduced SBP, tachycardy, sweating
70	M	12	100	Reduced SBP, flushing, headache, tachycardy, respiratory distress

SBP, systolic blood pressure.

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.

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European Journal of Cancer, Vol. 34, No. 8, pp. 1298–1299, 1998

Printed in Great Britain
0959-8049/98 $19.00+0.00

PII: S0959-8049(98)00066-5

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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Received 22 Dec. 1997; accepted 19 Jan. 1998.