4 × 300 mg/day was maintained (n = 3) or reduced to 4 × 250 mg/day (n = 1) because of dysrhythmia, hypotension and/or occurrence of chemotherapy-related grade 3/4 systemic toxicity.

1 out of 15 evaluable patients (7%), who had a pelvic recurrence of rectal cancer, had a partial response documented on computed tomography (CT) scan. Another 7 patients (47%) had stable disease for 3–7 months before disease progression. The median duration of survival of all patients entered on the protocol was 4.5 months (1.5–15+ months).

It would seem from our study results that despite histological demonstration of high levels of P-glycoprotein in colorectal cancer, we were unsuccessful in circumventing its clinical resistance to chemotherapy. There are several possible explanations for the disappointing therapeutic outcome: (1) overexpression of P-glycoprotein may be heterogeneous within a given population of tumour cells [8], (2) other resistance mechanisms may play a role, (3) bolus administration of doxorubicin might not have been optimal in terms of multidrug resistance modulation [9], (4) the dose of DVPM administered may have been inadequate to assure effective competition for binding sites in patients with large tumour volumes, and finally, (5) we can not exclude that our selection of pretreated patients for study might have adversely influenced the treatment outcome.

There was evidence from this trial that DVPM may increase some of the non-cardiac toxicity of doxorubicin. The observed levels of mucositis and myelotoxicity, frequently associated with infections, were quite different from the usually observed toxicity for single-agent doxorubicin at this dose. Whether this phenomenon might be related to inhibition of cytotoxic drug efflux from normal cells or through a pharmacokinetic interaction as suggested in a previous pilot pharmacokinetic study [10], we would suggest that careful consideration should be given to the anthracycline dose in future clinical studies using resistance modulators such as DVPM.

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Vascular Complications in Patients Treated with Granulocyte Colony-stimulating factor (G-CSF)

Albrecht Lindemann and Brigitta Rumberger

WITHIN 1 month we observed two unexpected sudden deaths in patients treated with granulocyte colony-stimulating factor (G-CSF). One of these was in remission from high-grade non-Hodgkin's lymphoma (NHL) after 7 weeks of therapy according to the VACOP-B regimen (etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin) [1], and had actually been treated with 3-day high-dose VIP (etoposide, ifosfamide, cisplatinum) [2] plus epirubicin 50 mg/m²/day for consolidation. The patient was in excellent condition 3 days post-treatment, with 18 700 peripheral blood cells (PBC)/μl and otherwise normal laboratory parameters. He received prophylactic norfloxacin, itraconazol and G-CSF 480 μg/day subcutaneously (s.c.) Early in the morning of the fourth day post-treatment he developed respiratory failure and cardiac arrest that was refractory to resuscitation. Autopsy revealed a moderate coronary sclerosis but no definite proof of ischaemia, and fatal arrhythmia was hypothesised.

The other patient suffered from intermediate grade NHL and had also received VACOP-B. Concomitant diseases were non-insulin-dependent diabetes and atherosclerosis, with a history of two myocardial infarctions and an ischaemic gangrene of the right hallux. Since he was neutropenic after the ninth week of treatment and exhibited signs of a local inflammatory response on his right foot, he was treated with intravenous (i.v.) antibiotics and G-CSF 300 μg/day s.c. The presumed infection disappeared within a few days. On the day of planned discharge (PBC 1900/μl, platelets 117.000/μl, normal coagulation profile), the patient experienced a myocardial infarction early in the morning, accompanied by cardiac failure that was refractory to intensive care unit treatment. Autopsy confirmed a thrombotic occlusion of a highly (>90%) stenotic right coronary artery.

Provoked by the close succession of these fatal events, we looked for possible common iatrogenic denominators. Although both patients had received G-CSF, pre-existing severe atherosclerosis (case 2) and toxicity of high-dose chemotherapy (case 1) may be regarded as sufficient explanation. However, Pettengell *et al.* [3] have reported an excess of vascular complications in G-CSF-treated patients in a randomised trial, although this has arbitrarily been attributed to higher doses of chemotherapy that could be administered to G-CSF-treated patients having received 95% of the planned dose as compared to 83% received by the controls. Furthermore, G-CSF has been implicated in the pathogenesis of arterial thrombosis in a recent case report [4].

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Different mechanisms may be operational in this regard. Thus, G-CSF has been shown to augment adenosine diphosphate-induced platelet aggregation *in vitro* and *in vivo* [5, 6]. Accordingly, a decrease in platelet counts has been observed in animals and humans [7, 8], which was dose-dependent and associated with elevated platelet factor-4 serum levels [8]. The dramatic upregulation of the neutrophil-endothelial cell homing receptor (LAM-1) affinity may be another pathogenetic factor [9]. Finally, direct effects on endothelial cell proliferation and migration have been reported [10]. Since these effects may have fatal consequences at sites of pre-existing lesions of the endothelium, specific attention regarding vascular complications during G-CSF therapy may be warranted in similarly predisposed patients.

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Breast Carcinoma Presenting with Inappropriate ADH Secretion

Andrew C. Howard, Robert W. Laing and Fez N. Hussain

A WOMAN PRESENTING with clinical and biochemical water intoxication (serum sodium of 118 mmol/l, potassium 4.6 mmol/l, urea 3.8 mmol/l, a serum osmolality of 250 mOsmol/kg and urine osmolality of 627 mOsmol/kg) was shown to have inappropriate secretion of antidiurectic hormone (ADH). Clinical examination and radiological investigation indicated a breast carcinoma to be the only possible source. Histopathological investigation of the tumour revealed a typical *in situ* ductal breast carcinoma with stromal invasion and regional lymph node metastases. Electron microscopy revealed neurosecretory granules in both primary and metastases, many cells staining positively with an argyrophil stain, and with antibody to ADH (Fig. 1). On removal of this tumour the patient's symptoms resolved and her biochemistry returned to normal. At 12 months she remains well with no local recurrence or evidence of further metastases.

Inappropriate ADH secretion is a rare condition most often associated with bronchial carcinoma, or with organic lesions of the hypothalamus and pituitary gland. We believe this to be the only histopathologically proven case of breast carcinoma causing inappropriate ADH secretion so far reported in the literature.

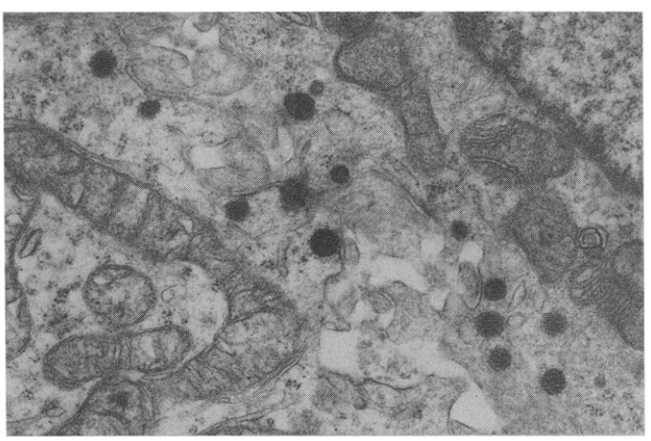

Fig. 1.

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