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Phase II Study of D-Verapamil and Doxorubicin in Patients with Metastatic Colorectal Cancer

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IN PATIENTS with disseminated colorectal cancer, systemic cytostatic treatment is widely used for palliation. However, the true benefit of chemotherapy for these patients, even with use of modern regimens based on biochemical modulation of 5-fluorouracil, remains uncertain in view of the low objective response rates, the limited, if any, survival benefits and the toxicity [1, 2]. Current discovery and development programs, therefore, need to be targeted at identifying new active agents and/or methods of improving the results with currently available drugs. Based on histological studies indicating that colorectal cancer expresses high levels of P-glycoprotein that might be related to its inherent refractoriness to conventional anticancer agents [3–5], and the promising therapeutic index of the second generation multidrug resistance modulator D-verapamil (DVPM) [6, 7], we have performed a phase II study of DVPM and doxorubicin in advanced colorectal cancer.

16 patients with measurable metastatic colorectal cancer were entered on to this study, all of whom had failed or relapsed after prior palliative 5-fluorouracil/leucovorin-based chemotherapy. Patients had to have histologically proven adenocarcinoma, WHO performance status of 0 or 1, white blood cell count (WBC) >4000/μl, platelet count >100 000/μl, serum bilirubin <1.5 mg/dl and serum creatinine <1.5 mg/dl. All patients had normal pretreatment electro- and echocardiograms (with a left ventricular ejection fraction of more than 50%), and resting systolic blood pressure (BP) >110 mmHg. All patients signed an institutionally approved consent for the treatment protocol. Treatment consisted of oral DVPM (Knoll AG, Ludwigshafen, Germany) given at a starting dose of 300 mg every 6 h for 3 consecutive days, and doxorubicin (75 mg/m^2) administered by intravenous bolus injection on day 2. Treatment was repeated every 3–4 weeks. If no cardiovascular symptoms occurred during the first treatment cycle, the dose of DVPM was increased to 4 × 350 mg/day. In case of chemotherapy-related WHO grade 3/4 systemic toxicity, the DVPM starting dose was maintained and the doxorubicin dose was lowered to 60 mg/m^2.

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Patients received a total of 47 courses of treatment (Table 1). 1 patient was considered inevaluable for response, since after discontinuation for doxorubicin-related acute cardiotoxicity during the first course, he refused further follow-up examinations. All other patients were assessable for response and toxicity.

Adverse reactions observed during this study consisted mainly of myelosuppression and cardiovascular side-effects: granulocytopenia with neutrophil counts below 500/μl was encountered in 10 patients (63%). 2 patients were hospitalised for granulocytopenic fever, and 6 others had minor febrile episodes. The median nadir neutrophil count was 810/μl (0–10, 488). Other severe haematologic side-effects included WHO grade 3–4 thrombocytopenia in 4 patients (median platelet count nadir 209 000/μl) and grade 3 anaemia, requiring erythrocyte transfusion, in 3 patients. Oral mucositis was observed in 8 patients (50%), other gastrointestinal side-effects were uncommon. DVPM-related cardiovascular symptoms occurred frequently, but never required active medical intervention or permanent discontinuation of therapy. Transient hypotension, defined as systolic BP <90 mmHg for at least one measurement, occurred in all 16 patients (36/47 treatment courses). Sinus bradycardia (<60 beats per min) was noticed in 8 patients (50%). First-degree atrioventricular block occurred in 5 patients (31%). Wenckebach block, auriculoventricular rhythm, and atrial ectopy were each observed in 1 patient. All dysrhythmias resolved within 2–3 h following temporary discontinuation of oral DVPM. 7 patients required modification of the dose of doxorubicin at some point during their treatment, primarily for haematological toxicity and/or stomatitis. The dose of DVPM was increased to 4 × 350 mg/day in 10 patients. In 4 patients the DVPM starting dose of

Table 1. Patients' characteristics

Number of patients	
Entered	16
Evaluable	15
Age (years)	
Median	59
Range	46–66
Sex	
Female	10
Male	6
Performance status	
WHO 0	12
WHO 1	4
Primary tumour site	
Colon	8
Rectum	8
Sites of metastases	
Liver	13
Lung	8
Abdominopelvic mass	7
Other*	2
Number of sites involved	
Single	5
≥2 sites	11

*Including bone in 1 patient and peripheral lymph nodes in 1 patient.

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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