course, 10 after the third course, 2 after the fourth course and 1 after the fifth course. Of these 19 withdrawals, 18 were because of no response to chemotherapy. 2 non-responders received four and five courses respectively, because computed tomography for response evaluaton was not done after the third cycle.

1 patient with a $T_4N_+M_0$ tumour who attained a PR after the fourth course did not receive further chemotherapy and had radical radiotherapy (60 Gy). He then achieved CR and remained disease-free 53 months after the start of chemotherapy. No patient withdrew because of toxicity.

There were 6 PRs for a response rate of 21% (95% CI 6–36%). 2 patients who responded had lung metastases and 4 locoregional advanced tumour. The mean duration of response was 7 months (range 4–12), excluding the patient who received radical radiotherapy after the fourth course. After carboplatin, 10 patients received doxorubicin and 5-fluorouracil; 1 patient had PR.

No treatment-related deaths occurred. There was no evidence of renal impairment caused by carboplatin nor any neurological toxicity. The most frequent side-effects were nausea, vomiting and myelosuppression (Table 1). 18 patients (64%) had haematological toxicity usually grade I or II; 4 patients had grade III and 1 had grade IV. All 5 severe toxicities were anaemia. 8 patients had grade I or II leukopenia, usually after courses 1–2, and 1 patient had grade II thrombocytopenia after the fourth course.

Thus carboplatin is moderately active in advanced bladder cancer. Other phase II trials gave response rates of 6–24% [7–9]. Carboplatin was well tolerated. Nausea and vomiting were the most frequent side-effects, which should be controllable by standard antiemetics. Myelosuppression was mild except in 5 patients with severe anaemia. Co-existing haematuria probably contributed to this major toxicity. We did not see significant leukopenia or thrombocytopenia, perhaps because the number of courses, (mean 3) was small. Since carboplatin can be administered to patients with poor renal function by dose attenuation and does not require extensive hydration outpatient administration is feasible.

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Epirubicin for Pretreated Advanced Ovarian Cancer

R. Coleman, K. Towlson, E. Wiltshaw, M. Slevin, P. Blake, R. Stein, R. Coombes and P. Harper

PROGNOSIS in recurrent epithelial ovarian cancer after chemotherapy with platinum analogues is poor.

In ovarian cancer doxorubicin has moderate activity in untreated patients [1] and has often been included in combination regimens [2]. However, toxicity and reduced activity in patients with platinum-resistant disease limits doxorubicin's value [3]. Epirubicin has similar activity in a variety of tumours [4] and may be less toxic [5]. Epirubicin has some activity in ovarian cancer [6] although as expected this was less in pretreated patients [7]. However, the dose of epirubicin may have been suboptimal since it is now clear that doses over 100 mg/m^2 may be given safely on a 3 weekly schedule. Our aim was to define the activity of epirubicin at the maximum tolerable dose in platinum-resistant ovarian cancer.

21 women with evaluable advanced epithelial ovarian cancer were studied. The median age was 55 (range 38–70). ECOG performance status was 4 patients (grade 0), 11 (grade 1), 5 (grade 2) and 1 (grade 3). All patients had progressed on previous platinum-based chemotherapy within the past 18 months and had bulky (over 2 cm diameter) disease. 18 patients had cystoadenocarcinoma and 3 had an endometroid tumour. Previous treatments were cisplatin (5), carboplatin (19), ifosfamide (5), medroxy-progesterone acetate (1) and radiotherapy (4). Sites of disease were intra-abdominal (21), lymph nodes (4), liver (8), lung (3) and spleen (2).

Epirubicin was given as a 5–10 min intravenous bolus every 21 days on an outpatient basis. Treatment was continued for six courses or until disease progression (or patient refusal). The median number of courses was two (range 1–6) with 4 patients receiving only one course. The starting dose of epirubicin was increased during the study from 90 mg/m^2 (8 patients) to 100 mg/m^2 (1 patient) to 110 mg/m^2 (12 patients). The dose in second and subsequent courses was based on day 10 and day 21 blood counts which allowed for dose reduction or escalation. No patient had the dose increased and 10 of 17 receiving more than one course required a reduction.

Assessment of response was by UICC criteria [8] and survival was calculated from the start of chemotherapy. The WHO scale [9] was used for toxicity.

Correspondence to R.E. Coleman, ICRF Medical Oncology Unit, Western General Hospital, Edinburgh, U.K.
R. Coleman, K. Towlson and P. Harper are at the ICRF Clinical Oncology Unit, Guy's Hospital, E. Wiltshaw and P. Blake are at the Royal Marsden Hospital, Fulham, M. Slevin is at the Homerton Hospital and R. Stein and R. Coombes are at the St Georges Hospital, London, U.K.

Table 1. Toxicity

	WHO grade					
	0	1	2	3	4	NK
White cell nadir						
90 mg/m²*	0	0	3	3	0	2
100 mg/m²*	0	0	1	0	0	0
110 mg/m²*	0	0	0	7	3	2
All doses†	0	0	3	11	5	2
Platelets						
90 mg/m²*	6	0	0	0	0	2
100 mg/m²*	1	0	0	0	0	0
110 mg/m²*	8	0	1	1	0	2
All doses†	17	0	1	1	0	2
Nausea and vomiting†	1	5	6	8	0	1
Alopecia†	2	3	5	10	0	1
Stomatitis†	12	6	1	1	0	1

*First course.
†Worst course.
NK = not known.

No patients had an objective response. 1 patient had a subjective response with improvement in performance status. 3 patients did not progress on treatment (no change response category) but 2 of them progressed within 6 weeks of completing chemotherapy. The median duration of survival was 5 months (range 1–11) and 16 (76%) patients have died. There were no treatment-related deaths.

Toxicity is summarized in Table 1. The dose-limiting toxicity was neutropenia with a nadir white cell count below 2.0×10^9/l in all patients treated with 110 mg/m² of epirubicin. In view of this and the lack of response higher doses of epirubicin were not tested. The treatment caused significant alopecia in 15 patients despite scalp cooling. Nausea and vomiting were troublesome in 14 patients despite prophylactic anti-emetics.

Epirubicin had at best minimal activity in platinum-resistant ovarian cancer. Despite increasing the dose to the maximum tolerated dose, there were no objective responses. Bone marrow suppression was the dose-limiting toxicity and was often severe, leading to dose reductions. Subjective toxicity was significant with nausea, vomiting, anorexia and alopecia all detracting from the quality of life.

Alternative approaches to the treatment of relapsed ovarian cancer are urgently needed but it seems unlikely that any of the currently available cytotoxic agents will be of benefit. Patients with platinum-resistant ovarian cancer are therefore an ideal group for the testing of new drugs. There is no indication for the use of epirubicin, even at high doses, in ovarian cancer patients after exposure to a platinum compound.

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Unresponsiveness of Pancreatic Adenocarcinoma to Antioestrogen Therapy

W. Scheithauer, G. Kornek, K. Haider and D. Depisch

A NEW APPROACH to the treatment of advanced pancreatic carcinoma was suggested in 1981 with the demonstration of sex hormone receptors in these tumours [1]. Confirmation of this finding in human and in experimentally induced murine tumours [2, 3], as well as demonstration of the inhibiting effect of hormonal manipulation on the growth of human pancreatic adenocarcinoma xenografts in nude mice [4], stimulated clinical evaluation. Encouraging preliminary results were observed in small uncontrolled studies, mainly with tamoxifen [5–7]. Since some phase III trials were started but not reported, we decided to re-evaluate this therapeutic concept.

26 consecutive patients with pathologically confirmed advanced adenocarcinoma of the pancreas that was not potentially curable by surgery entered the study between May 1988, and August 1989 (Table 1). 19 patients had a laparotomy for biopsy, palliative bypass procedures, or partial pancreatectomy and 7 patients had the diagnosis established by ultrasound-guided needle biopsy without laparotomy. Previous treatment had to be completed at least 6 weeks before entry. Informed consent was obtained in all patients.

Correspondence to W. Scheithauer, Department of Gastroenterology II, Vienna University Medical School, Garnisongasse 13, A-1090 Vienna, Austria.
W. Scheithauer and G. Kornek are at the Department of Gastroenterology II, Vienna University Medical School, Vienna; and K. Haider and D. Depisch are at the Department of Surgery, Wr. Neustadt Hospital, Austria.