The timing and number of episodes of vomiting and retching were recorded and cross-checked with the patient. Nausea was assessed on a 100 mm visual analogue scale (VAS), 0 mm representing 'felt not at all sick' and 100 mm representing 'worst ever feeling of sickness'. One emetic episode was defined as any vomit productive of liquid or one to five retches within 5 min. On days 2–6, a single retch was considered as one emetic episode. A complete response (CR) was defined as no emetic episodes, a major response as (MR) zero to two episodes and a minor response (mR) as three to five episodes. Failure (F) was defined as more than five emetic episodes or that rescue therapy was necessary.

Forty-three patients were evaluable. During the acute phase (first 24 h) sixteen patients (37%) had a complete response, eleven (26%) a major response and six (14%) a minor response, ten patients (23%) failed. In the sixteen patients refractory to prior treatment the response was: CR in three patients, MR one, mR four and F in eight patients. Almost complete control of nausea (VAS $\leq$10 mm) was achieved in seventeen patients (40%). No dose–response with this broad dose range was detected.

In the delayed phase (days 2–6) twenty-eight patients were included. Nine (32%) patients had a complete response, six (21%) a major response and four (14%) a minor response. Nine patients (32%) failed. Diary cards on nausea were not completed for 1 or more days in nine patients. Therefore, these data were not analysed in detail.

Headache (22%) and constipation (16%) were the main side-effects reported and these were generally mild. No major sedative or extrapyramidal side-effects were observed. When questioned at follow up, twenty-two out of twenty-eight patients (79%) wanted ondansetron treatment if they were to receive chemotherapy again.

Ondansetron was effective and well tolerated over a broad dose range in the prevention of cisplatin-induced emesis. However, efficacy in the prevention of delayed emesis remains unclear.

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Eur J Cancer, Vol. 26, No. 6, pp. 770–771, 1990.
Printed in Great Britain
0277–5379/90$3.00 + 0.00
Pergamon Press plc

Octreotide and Bromocriptine in Patients with Stage D2 Prostate Cancer who Relapsed during Treatment with Flutamide and Castration

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LUTEINISING-HORMONE releasing hormone (LHRH) analogues have an increased inhibitory effect on the growth of the Dunning prostate adenocarcinoma when combined with a somatostatin agonist [1]. Thus, 11 patients with progression of disseminated prostate cancer while receiving the LHRH agonist (D-Trp^6, des-Gly-NH$_2^{10}$)LHRH ethylamide (250 μg subcutaneously daily) or surgical castration in association with flutamide (250 gm, every 8 h orally) also received octreotide and bromocriptine. Octreotide was administered subcutaneously under constant infusion with a model AS-6C syringe pump (Travenol). The starting daily dose was 600 μg with a stepwise increase until a daily dose of 1350 μg was reached after 1 week. Bromocriptine was started on the second week and given at 2.5 mg every 12 h orally. The average duration of treatment for the 10 evaluable patients was 75.1 days (range 21–114).

None of the 10 evaluated patients had a positive objective response assessed by the NPCP criteria [2] after the addition of octreotide and bromocriptine. Three of the patients discontinued treatment because of rapid deterioration of disease after 21, 39 and 48 days, respectively; these patients died 58, 220 and 78 days later. All the other patients showed signs of deterioration at bone scintigraphy 3 months after starting treatment with octreotide and bromocriptine. Seven patients died at 58, 78, 90, 158, 164, 220 and 350 days after stopping octreotide and bromocriptine. The three surviving patients continued to progress despite the addition of aminoglutethimide and hydrocortisone.

The decrease in plasma growth hormone concentration was not significant during the daily administration of an average of 1350 μg octreotide and 5 mg bromocriptine. Serum prolactin and IgF, on the other hand, significantly decreased after 1 month of treatment and remained low for up to 3 months; insulin and glucagon levels changed similarly.

The early termination of this phase II trial, in which the sample size had been fixed at 19, was mainly caused by rapid evolution of disease during treatment with octreotide and bromocriptine. The number and/or size of bone lesions increased in all patients except one. In this patient disease progression was

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suggested by an increase in serum prostatic acid phosphatase and serum prostate-specific antigen from 6.4 to 24 ng/ml and from 96 to 180 ng/ml, respectively.

The accrual of 53% of the planned sample (10/19) yields a P value of 0.19 instead of the previously fixed 0.05. Interim analysis shows that any hypothesized response rate of 26% or more is rejected at the 0.05 one-sided level of significance [3]. With Hilsenbeck's method there will have been an 81% chance at the end of the completed study that the 95% confidence intervals for the true response rate would fail to include improvement rates of 30% or more [4]. Similar results were obtained by Dr C. Logothetis (personal communication).

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Eur J Cancer, Vol. 26, No. 6, p. 771, 1990.
Printed in Great Britain
0277-5379/90$3.00 + 0.00

Treatment of Advanced Ovarian Cancer with Intraperitoneal Tumour Necrosis Factor

J. Hardy, A. Jones, M.E. Gore, C. Viner, P. Selby and E. Wiltshaw

TUMOUR NECROSIS FACTOR (TNF) is active *in vivo* when used intraperitoneally against human ovarian xenografts [1, 2]. Intraperitoneal administration of drugs in ovarian cancer is attractive for three reasons: patients have disease limited to the peritoneal cavity [3], there may be less systemic toxicity when drugs are given by this route and tumour cells may be exposed to higher concentrations of drug for longer. There is *in vitro* evidence that such prolonged exposure is required for TNF-induced cytoxicity [4]. We report our results of intraperitoneal TNF in ovarian cancer.

Patients with advanced epithelial ovarian cancer, refractory to cisplatin, were eligible if they had ascites, evaluable disease, projected survival greater than 2 months and had given informed consent. Exclusion criteria included leucopenia ($< 3.5 \times 10^9$/1), thrombocytopenia ($< 100 \times 10^9$/1), hepatic/renal dysfunction (unless due to metastases) and WHO performance status of 3–4. Patients had not received previous biological therapy and had not had chemotherapy for at least 2 weeks. Patients' details are shown in Table 1.

Abdominal paracentesis was done with a 14 *G* Abocath or dialysis catheter and the peritoneal cavity was drained to dryness. TNF (Asahi Chemical Co.) 2×10^5 U (89 μg)/m^2 was dissolved in 1 l normal saline and infused over 1 h via the paracentesis catheter. This was then clamped for 24 h after which any remaining ascites was drained and the catheter removed. Patients were rotated to ensure even distribution of TNF. Ketoprofen 100 mg was used prophylactically to reduce febrile reactions and established fevers were treated with paracetamol and pethidine. Treatment was repeated 4 weekly. Patients were assessed clinically once a week and by ultrasound or computerised axial tomography before each course.

Table 1. Patients' characteristics and toxicity and outcome of intraperitoneal TNF

	Patient			
	1	2	3	4
Age	45	59	49	38
Performance status	1	2	1	0
No. of courses	4	3	1	3
Acute toxicity (fever, etc.)	+	+	+	+
Abdominal pain/peritonism	+	+	+	+
Infection*	+	–	–	+
Response	PD	PD	PD	PD

*Cellulitis in case 1 and septicaemia in case 4.
PD = progressive disease.

The four patients received a total of eleven courses (Table 1). All patients developed pyrexia (temperature over 38°C), influenza-like symptoms and abdominal discomfort during infusion. Peritonism developed in six courses, one patient had gram negative septicaemia (*Escherichia coli*) not associated with leucopenia and one developed cellulitis of the abdominal wall due to leakage of infusate along the catheter tract. All patients had malaise for about 2 weeks. There were no objective responses.

The toxicity of intraperitoneal of TNF includes acute systemic symptoms similar to those reported after intravenous administration [5]. In addition, all patients complained of abdominal pain and peritonism was observed in over half the courses given. High doses of TNF can be given intraperitoneally to mice without clinical or histological evidence of peritonitis (A.J.). In man intraperitoneal TNF is not well tolerated even at doses well below the maximum tolerated intravenous dose (440 μg/m^2).

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