Eur J Cancer Clin Oncol, Vol. 23, No. 8, pp. 1219–1223, 1987.
Printed in Great Britain

0277-5379/87$3.00+0.00

Letter to the Editor

Establishment of Human Ovarian Tumour Lines in Nude Mice and their Responses to Platinum Analogues

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AMONG the large number of platinum analogues, *cis*-diammine-1,1-cyclobutane dicarboxylate platinum II (CBDCA) and *cis*-dichloro-*trans*-dihydroxy-bis-isopropylamine platinum IV (CHIP) have been selected as promising compounds and projected for clinical trials [1, 2]. There have been several clinical reports describing the antitumour activity of platinum analogues against ovarian cancer [3–7]; however, the responses of such cancers to these drugs, according to tumour histological types, have been unclear. We have established three different histological types of ovarian cancer in nude mice and, using the human tumour–nude mouse panel system, have examined the antitumour activity of platinum analogues in comparison with that of *cis*-diamminedichloro platinum II (CDDP).

For tumour transplantation, tumour tissue collected aseptically at operation was sectioned to pieces of 2–3 mm^3 in Eagle's minimum essential medium. Using a trocar needle, the tumour tissue fragments were transplanted subcutaneously into the dorsal area of female BALB/c nude mice. The transplants all grew as solid tumours at the inoculation site. Pathological examination revealed that histology of the OVA-1 tumour, resected at the operation, was mucinous cystadenocarcinoma, the OVA-3 tumour was endometrioid adenocarcinoma and OVA-4 tumour was serous cystadenocarcinoma. The transplanted tumours were histologically similar in appearance to those in the original patients. Tumour cells showed the characteristic appearance of each tumour (Fig. 1). For marker assays, CEA and CA 125 levels in the sera of tumour-bearing mice were measured using a CEA RIA kit (Dainabot, Chiba, Japan) and a CA 125 kit (Cis, Saclay, France). Elevated levels of CEA (660 ng/ml) were maintained in the sera of OVA-1 tumour-bearing nude mice. Also, elevated levels of CA 125 were detected in the sera of OVA-3 tumour-bearing nude mice (164 U/ml) and OVA-4 tumour-bearing nude mice (12800 U/ml), respectively. These newly established heterotransplanted tumours (OVA-1, OVA-3 and OVA-4) preserved the ability to produce marker proteins specific to their respective histologies.

The newly established ovarian tumours (OVA-1, OVA-3 and OVA-4) and poorly differentiated adenocarcinoma (OVA-2) were used for chemotherapeutic studies. The characteristics of the OVA-2 tumour were previously described [8].

CBDCA was supplied by the Drug Synthesis and Chemistry Branch, National Cancer Institute, U.S.A. CHIP and CDDP were supplied by Bristol-Myers Company. CDDP was dissolved in 0.2 ml 0.9% NaCl solution and CBDCA and CHIP were dissolved in 0.2 ml distilled water. Fifty mg/kg of CBDCA, 25 mg/kg of CHIP and 6 mg/kg of CDDP were administered intraperitoneally into tumour-bearing nude mice three times with inter-

Accepted 16 March 1987.
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Table 1. Summary of the effect of CDDP, CBDCA and CHIP on human ovarian cancers heterotransplanted in nude mice

Tumour line	Treatment	No. of mice	*T/C* volume (*P**)	(Day)
OVA-1	NaCl (controls)	6		
	CDDP	9	51.3 (NS)	(16)
	CBDCA	10	18.6 (< 0.05)	(24)
	CHIP	9	20.9 (< 0.05)	(27)
OVA-2	NaCl (controls)	10		
	CDDP	6	27.7 (< 0.01)	(24)
	CBDCA	6	35.3 (< 0.01)	(36)
	CHIP	7	25.3 (< 0.001)	(32)
OVA-3	NaCl (controls)	10		
	CDDP	5	10.9 (< 0.01)	(28)
	CBDCA	8	92.0 (NS)	(19)
	CHIP	10	69.0 (NS)	(15)
OVA-4	NaCl (controls)	6		
	CDDP	7	5.4 (< 0.05)	(28)
	CBDCA	7	4.5 (< 0.05)	(25)
	CHIP	5	47.9 (NS)	(29)

*Analysis was performed for control group vs. treated groups, with the use of Student's *t*-test. NS: not statistically significant.

vals of 4 days. Control mice were injected intraperitoneally with 0.2 ml 0.9% NaCl.

When the tumours became palpable and were growing progressively, experimental mice were randomized into test groups of 5–10 mice (one tumour each). The size of the implant was measured with slide calipers twice a week, and the volume (V), in mm^3, was calculated by means of the formula described by Houchens *et al.* [9], $V = W^2 \times L \times 1/2$, where W is the width in mm and L the length in mm.

A summary of the effect of CDDP, CBDCA and CHIP on human ovarian tumours heterotransplanted in nude mice is shown in Table 1. Treatment of the OVA-1 tumour was initiated 47 days after transplantation. CDDP did not significantly affect the growth of OVA-1. On the other hand, CBDCA and CHIP both significantly suppressed the growth of OVA-1. Treatment of the OVA-2 tumour was initiated 27 days after transplantation. CDDP, CBDCA and CHIP all significantly suppressed the growth of OVA-2. No statistical difference in the antitumour activity of these drugs was observed between CDDP-, CBDCA- and CHIP-treated groups. Treatment of the OVA-3 tumour was initiated 34 days after transplantation. CDDP suppressed tumour growth. The tumour disappeared in two out of five mice treated with CDDP. However, CBDCA and CHIP did not affect the growth of the OVA-3 tumour. Treatment of the OVA-4 tumour was initiated 10 days after transplantation. CDDP and CBDCA both significantly suppressed the growth of the OVA-4 tumour. The tumour disappeared in one of seven mice treated with CDDP and in one of seven mice treated with CBDCA. However, CHIP did not affect the growth of the OVA-4 tumour. The largest decrease (15%) in mean body weight was observed on days 10–15, though the decrease was not statistically different between the CDDP-, CBDCA- and CHIP-treated groups.

We have previously reported that two (YST-2, YST-3) xenografted yolk sac tumours exhibited broadly comparable sensitivity to CDDP and its two analogues, with YST-1 being substantially more sensitive to CDDP than to CBDCA or CHIP [10]. In this experiment, as shown in Table 1, among three platinum analogues, CDDP broadly showed effective antitumour activity against epithelial ovarian cancer. However, mucinous cystadenocarcinoma (OVA-1) did not significantly respond to CDDP, though it responded well to CBDCA and CHIP. Our preliminary data suggest that the antitumour activity spectrum of platinum analogues may differ from that of the parent drug compound CDDP.

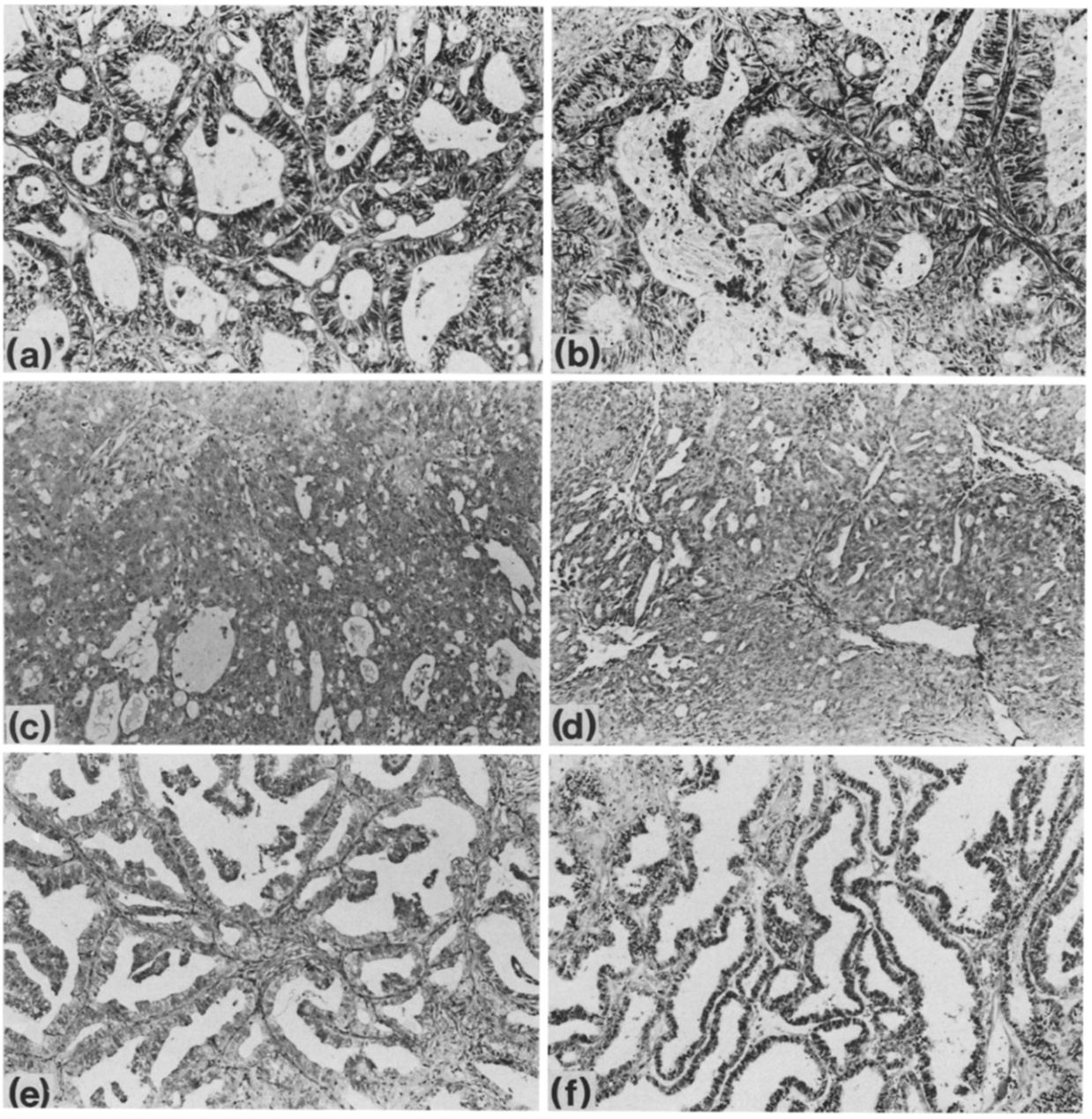

Fig.1. Histological appearance of mucinous cystadenocarcinoma (OVA-1) grown in nude mice (a), with the original tumour (b). Histological appearance of endometrioid adenocarcinoma (OVA-3) grown in nude mice (c), with the original tumour (d). Histological appearance of serous cystadenocarcinoma (OVA-4) grown in nude mice (e), with the original tumour (f). (Haematoxylin and eosin, × 53).

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