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Response from Rudas and Associates

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WE REGRET that our article gave rise to the assumption that we divided the intraductal carcinomas of the breast into two groups. In fact, we followed the classification proposed by the EORTC which divides the DCIS into three groups: high differentiated, intermediate differentiated and low differentiated DCIS. The most important criterion for classification is the grade of pleomorphism of the tumour cell nuclei. In the group of low differentiated DCIS, necrosis is also included in the classification.

From our experience, nuclear pleomorphism is a very important criterion for classification; necrosis is mostly associated with high nuclear pleomorphism and is therefore most common in the group of low differentiated DCIS.

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Combined Effects of Cisplatin and *N*, *N*-Diethyl-2-[4-(Phenylmethyl)Phenoxy] Ethanamine HCl on the Growth of Human Ovarian Cancer Xenografts in Nude Mice

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WE DEMONSTRATED in a previous report that when low doses (5 and 10 mg/kg) of *N,N*-diethyl-2-[4-(phenylmethyl)phenoxy]ethanamine·HCl (DPPE) were combined with cisplatin (CDDP), survival was significantly improved without inhibition of tumour growth in nude mice bearing human ovarian cancer xenografts (KF cells) [1]. In addition, a preliminary clinical trial in refractory cancer patients indicated a possible benefit from DPPE in combination with various single antineoplastic agents [2,3]. However, potentiation of antitumour activity of CDDP by DPPE has not yet been defined. Thus, we attempted to determine the inhibitory effects of high doses of DPPE and its combination with CDDP on the growth of human ovarian cancer cell tumours in nude mice.

To determine the combined effects of high doses of DPPE and CDDP on tumour growth, 5×10^5 KF cells were inoculated subcutaneously (s.c.) into the right flank of nude mice. From 14 days after tumour inoculation, treatment with CDDP and DPPE was initiated. Treatment with DPPE and CDDP was performed as follows: control group (n=10), medium alone was administered intraperitoneal (i.p.) once a week for 6 weeks; DPPE (25 mg/kg)-treated group (n=10), 25 mg/kg DPPE alone was administered i.p. once a week for 6 weeks; DPPE (50 mg/kg)-treated group (n=10), 50 mg/kg DPPE alone was administered i.p. once a week for 6 weeks; CDDP-treated group (n=10), 2 mg/kg CDDP alone was administered i.p. once a week for 6 weeks; DPPE (25 mg/kg)+CDDP treated group (n=10), 25 mg/kg DPPE and 2 mg/kg CDDP were simultaneously administered i.p. once a week for 6 weeks; DPPE (50 mg/kg)+CDDP treated group (n=10),

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Table 1. Effects of high-dose DPPE and CDDP on the tumour growth of KF cells inoculated into nude mice

Treatment	Days after tumour inoculation						
	21	28	35	42	49	56	63
Control	0.9±0.2*	1.9±0.5	2.6±0.8	5.4±1.3	7.1±2.1	7.6±1.8	8.0±2.4
DPPE (25 mg)	1.1±0.2	1.7±0.6	2.4±0.5	4.0±0.9	4.7±1.2†	6.2±2.0	7.0±1.8
DPPE (50 mg)	0.5±0.2†‡	0.8±0.4†‡	1.2±0.6†‡	2.1±0.8†‡	3.0±1.5†‡	5.9±1.7†	6.9±2.0
CDDP	1.0±0.3	1.8±0.6	2.4±0.7	4.3±1.0	4.9±1.5†	5.7±1.9†	6.4±1.0†
CDDP+DPPE (25 mg)	0.3±0.1	0.4±0.2§	0.6±0.3§	1.0±0.5§	2.0±1.1§	3.5±1.9§	5.9±1.8
CDDP+DPPE (50 mg)	0.5±0.2	0.7±0.3‡	1.0±0.5‡	1.5±0.6‡	2.5±1.2‡	5.3±1.8	6.3±1.5

Each group consisted of 10 mice. Treatment was performed once a week for 6 weeks from 14 days after tumour inoculation. *Tumour volume (cm^3); mean±S.D. †$P<0.05$, compared with negative controls. ‡$P<0.05$, compared with CDDP-treated controls. §$P<0.05$, compared with both CDDP-treated and DPPE (25-mg)-treated controls.

50 mg/kg DPPE and 2 mg/kg CDDP were simultaneously administered i.p. once a week for 6 weeks. Each injection was given in a 0.15 ml volume. Tumour growth was determined by the measurement of diameters of the tumour nodule in two dimensions with a caliper once a week. The tumour volume (cm^3) was calculated as described in a previous paper [2]. Blood from a tail vein was collected into haematocrit tubes every week and the haematocrit values and body weight were recorded for monitoring the side-effects of the drugs. The results were presented as the mean ± S.D. Statistical analysis of the results was performed using Student's *t*-test and analysis of variance.

Treatment with 25 mg/kg DPPE only inhibited tumour growth 49 days after tumour inoculation compared with negative controls, while 50 mg/kg DPPE only significantly inhibited tumour growth during the whole treatment period (from day 21) compared with both negative and the CDDP-treated controls (Table 1). When CDDP was combined with DPPE, 25 mg/kg DPPE was more potent than 50 mg/kg with regard to inhibition of tumour growth (Table 1). Although high doses of DPPE used in this study did not show any serious adverse effect, 50 mg/kg DPPE seemed to have a tendency of lowering the haematocrit and body weight (data not shown). In conclusion, DPPE, a unique agent with both antihistamine and anti-oestrogenic actions, increases the therapeutic index of CDDP and may be of use for the treatment of refractory ovarian carcinoma.

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Paclitaxel in Recurrent Ovarian Cancer: Better Upfront? Comments On: A Phase II Study of Paclitaxel in Platinum Pretreated Ovarian Cancer. A Hellenic Cooperative Oncology Group Study. *Eur J Cancer* 1977, 33, 160–163.

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The Hellenic Cooperative Oncology Group (HeCOG) have highlighted an interesting situation with regard to the use of paclitaxel in ovarian cancer [1]. Though the numbers were small, it is interesting to note that both the response rates and the median survival were better in the subgroup of patients who received paclitaxel on first relapse. This does raise some fundamental questions about the optimum duration and timing of paclitaxel chemotherapy in the management of ovarian cancer. The earlier studies in heavily pretreated patients, despite confirming the activity of the drug in this cancer, showed that the complete response (CR) rates were relatively low and the time to progression was also much shorter. The NCI overview of 1000 platinum refractory

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