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.

V.R. Bulusu

Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ, U.K.

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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ovarian cancer patients and the U.K. and Eire group study of paclitaxel had one thing in common, low complete response rates (4 and < 2%, respectively) to single-agent paclitaxel at a 175 mg/m^2 3-h infusion schedule in the advanced/recurrent situation [2, 3].

Though there seems to be a reasonable consensus with regard to the dose/schedule of paclitaxel in combination with a platinum (carboplatin or cisplatin) compound, one aspect which is yet to be clearly defined is the timing of paclitaxel. The only randomised trial so far which has shown a survival advantage for patients exposed to upfront paclitaxel and platinum is the GOG 111 study [4]. In this trial very few of the patients who were on the control arm i.e. cisplatin + cyclophosphamide, were offered paclitaxel at relapse. The GOG have settled for a paclitaxel dose of 175 mg/m^2 for their subsequent studies. However, it is important to remember that the issue of dose and schedule is not yet fully resolved. There is some evidence to suggest that one might see responses with a more prolonged (96-h) infusion when shorter infusion schedules have failed to elicit a response [5].

Our experience with single-agent paclitaxel in recurrent ovarian cancer has been disappointing [6]. Most of our patients had paclitaxel as a second- or third-line therapy. In this scenario as expected both the response rates and the duration of response were lower. This mirrors the U.K. and Eire group experience wherein the overall responses were < 25% with a median survival of under 10 months [3]. Also in our study and in the other trials, the median number of cycles was around 4 and 90% of the patients received a maximum of 6. It is interesting to note that the HeCOG have continued beyond six cycles in patients who were responding to paclitaxel. This may be an important factor in the use of paclitaxel, both in the induction and the recurrent setting. Paclitaxel might have an initial cytocidal effect followed by a cytostatic effect on continued exposure, thus resulting in a longer time to progression.

Another variable which might be clinically relevant, influencing the response to paclitaxel in the recurrent scenario, is the development and or modulation of taxane resistance due to prior exposure to other cytotoxic agents. In our patient group, prior exposure to the podophyllotoxin, etoposide seemed to result in a lower response to subsequent challenge with paclitaxel. The mechanism of this interaction is poorly understood. The probable explanation for this phenomenon includes altered microtubular framework, rendering paclitaxel relatively ineffective and/or other unknown mechanisms.

The EORTC trial comparing cisplatin and cyclophosphamide versus cisplatin and paclitaxel is particularly relevant because the patients in the control arm are randomised to receive paclitaxel on first relapse. In addition, the MRC ICON4 trial comparing paclitaxel and platinum combination with single-agent platinum at first relapse will also be addressing this important issue of the timing of paclitaxel. Both trials incorporate quality-of-life assessments as endpoints, in addition to survival. If these two large randomised trials show that the overall survival is not significantly different whether paclitaxel is used upfront as part of initial induction or on first relapse, this would have considerable impact on the way one targets ovarian cancer with taxenes. Also, the cost implications of such a result, as one might envisage, are quite significant. In addition, such a result may also help to define a subgroup of patients who are most likely to gain the maximum potential benefit of taxenes.

The question of optimal timing of paclitaxel in epithelial ovarian cancer is yet be resolved. Paclitaxel should be used judiciously to realise the full potential of this otherwise effective drug in ovarian cancer.

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