Comparative Efficacy of Platidiam and Carboplatin Against Tumor Cells of Human Ovarian Primary Carcinomas

I. K. Sviridova, N. S. Sergeeva, V. I. Chissov, V. A. Kirsanova, A. V. Babarina, E. G. Novikova, and G. A. Obrubova

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny,* Vol. 120, No. 8, pp. 208-210, August, 1995
Original article submitted September 6, 1994

The efficacies of platidiam and carboplatin against human ovarian cancer cells (21 samples) were compared using *the in vitro* MTT test. Sampling analysis showed a somewhat higher mean activity of carboplatin in comparison with platidiam in the dose range equivalent to 0.1 to 3.0 therapeutic doses. The efficacy of carboplatin was found to increase more rapidly with dosage build-up than that of platidiam.

Key Words: *experimental chemotherapy; human ovarian carcinoma cells; cytostatic dose-effect curves*

Chemotherapy is a key component in the treatment of human ovarian cancer [7]. Platidiam is considered to be one of the most effective drugs for tumors of this type [2,5]. Recently, platidiam analogs have begun to be used in oncogynecology, one of them being carboplatin [1,8]. The efficacy of platidiam derivatives has been studied *in vitro* on primary cell cultures derived from tumors of the lungs [10], head and neck [9], and other sites [4,6]. However, the efficacy of these agents in ovarian cancer has practically not been studied.

In this study we compared the efficacies of platidiam and carboplatin against human ovarian primary carcinoma cells.

MATERIALS AND METHODS

Ten samples of human ovarian carcinoma tissue (surgical material) and 11 samples of ascitic fluid obtained by paracentesis from patients with ovarian cancer were the sources of tumor cells (a total of 21 patients were thus examined). Cells were isolated from ovarian carcinoma tissue by mechanical and enzymatic disintegration [3]. The suspension was filtered through a series of sieves with pore diameters of 60 to 120 mm (Sigma), after which the filtrate was washed three times in RPMI-1640 incubation medium (Serva) with 10% fetal calf serum (Gamaleya Research Institute of Epidemiology and Microbiology, Russian Academy of Medical Sciences, Moscow), 2 mM glutamine, 10 μg/ml gentamicin, and 25 mM HEPES (Sigma), and the cells were precipitated by centrifugation. Tumor cells from the ascitic fluid were isolated by 10-min centrifugation at 1000 rpm after the addition of 10 U/ml heparin. Viable tumor cells were counted and their share was assessed in a Goryaev chamber after the addition of 0.2% trypan blue (Serva) at all stages of the study. All procedures were performed under sterile conditions. Then tumor cells in a concentration of 5×10^4 per well were incubated for 72 h with the cytostatics in 96-well Linbro plates in an atmosphere with 5% CO_2. The efficacy of the cytostatics was assessed by their influence on tumor cell dehydrogenase activity using the MTT test, the amount of formazan produced by the cells being measured with an MCC-340 spectrophotometer (Labsystems) [3]. Tetrazolium salt 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT, Sigma) was used as substrate. The final concentrations of the cytostatics in the incubation

P. A. Hertzen Research Oncological Institute, Moscow

0007-4888/95/0008-0851$12.50

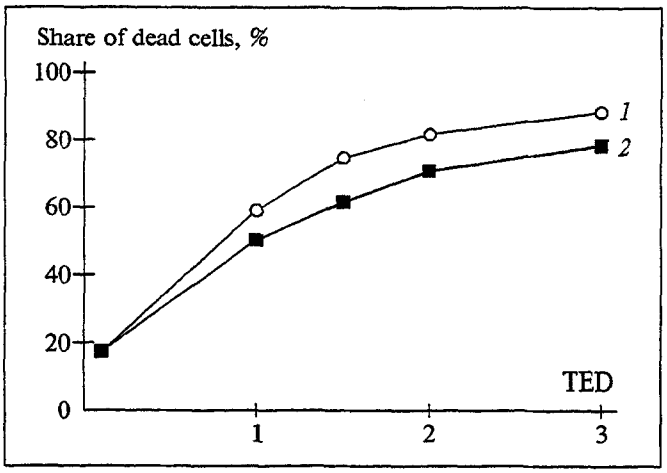

Fig. 1. Relationship between the mean share of dead ovarian carcinoma cells and the dose of platidiam (*2*) and carboplatin (*1*).

medium ranged from 0.1 to 3.0 therapeutically equivalent doses (TED); for platidiam 1.0 TED was 6 μg/ml, and for carboplatin 50 μg/ml [3]. The data were represented in "cytostatic dose - effect" coordinates (share of dead cells), it being assumed that the percentage inhibition of the intensity of redox processes in tumor cells is proportional to the share of dead cells [3]. The drug was considered effective against the tumor if it caused the mortality of at least 50% of cells.

RESULTS

Comparative analysis of the 21 pairs of dose-effect curves plotted using the MTT test for platidiam and carboplatin showed that the mean efficacy (for the whole sample) of both cytostatics increased with their dosage build-up from 0.1 to 3.0 TED, carboplatin being somewhat more effective than platidiam in all the doses tested (Fig. 1).

Figure 2 shows histograms of tumor distribution by the share of cells killed by platidiam and carboplatin used in equivalent doses. The histograms virtually coincide at platidiam and carboplatin doses corresponding to 0.1 and 1.0 TED. Doses corresponding to 0.1 TED caused the death of no more than 25% of cells in the majority (more than 70%) of cases (Fig. 2, *a*), whereas at doses corresponding to 1.0 TED (Fig. 2, *b*) the number of cases with a variously expressed cytotoxic effect was approximately the same for both platidiam and carboplatin. At higher doses of the agents (1.5 to 3.0 TED) the efficacy of carboplatin increased appreciably more than that of platidiam (Fig. 2, *c-e*). At doses equivalent to 3.0 TED the proportion of cases where the drug caused the death of more than 75% of tumor cells was substantially and reliably higher for carboplatin than

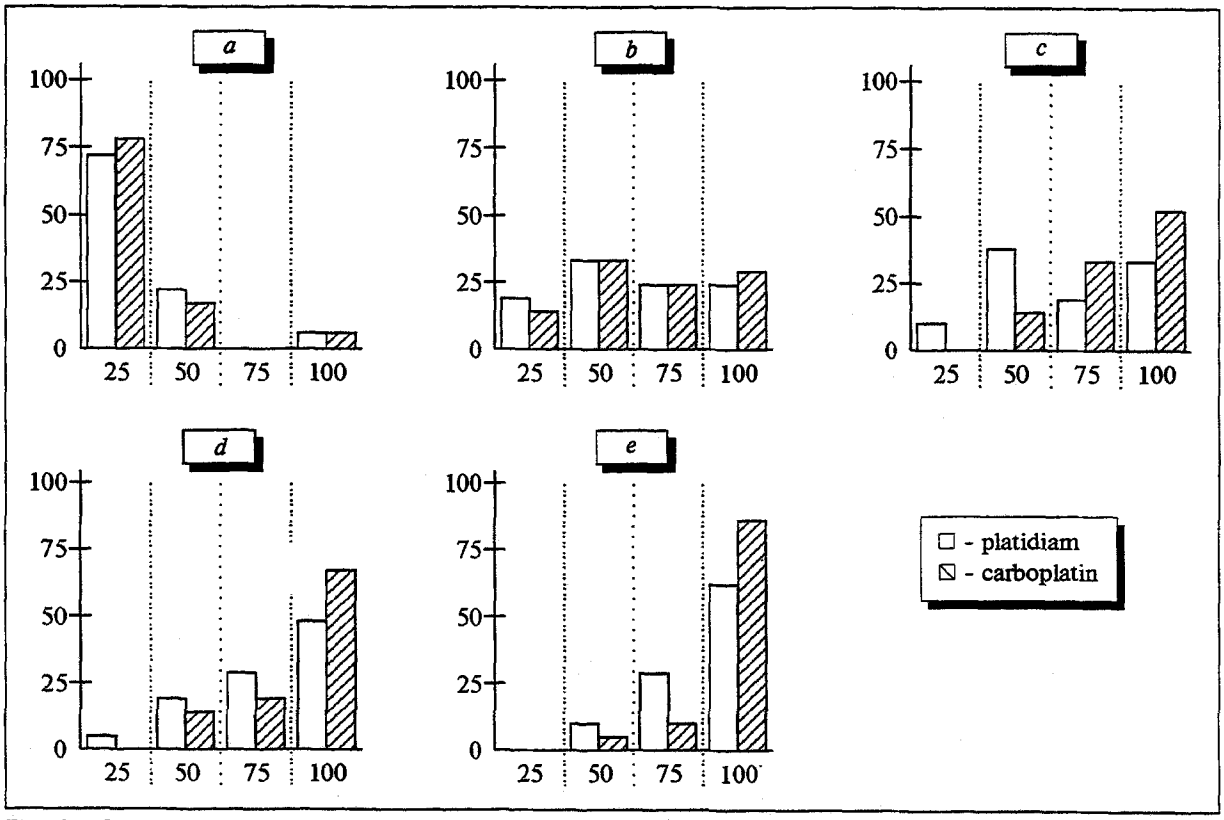

Fig. 2. Distribution histograms of ovarian carcinomas showing the share of dead cells at platidiam and carboplatin doses of 0.1 (*a*), 1.0 (*b*), 1.5 (*c*), 2.0 (*d*), and 3.0 (*e*) TED.

TABLE 1. Comparative Efficacy of Platidiam *vs.* Carboplatin Against Human Ovarian Carcinoma Cells (in %)

Carboplatin/ platidiam	Drug dose, TED				
	0.1	1.0	1.5	2.0	3.0
r/r	72.2±10.6	9.5±6.4	14.3±7.6	4.8±4.7	4.8±4.7
s/s	–	23.8±9.3	52.4±11.9	52.4±11.9	57.1±12.0
r/s	5.6±5.4	38.1±10.6	0	4.8±4.7	4.8±4.7
s/r	22.2±9.8	28.6±9.9	33.3±10.3	38.1±10.6	33.3±10.3

Note. *r*: resistance, *s*: sensitivity.

for platidiam (86±7.6 and 62±10.6%, respectively, Fig. 2, *e*).

This conclusion is confirmed by comparing the ratio of tumors sensitive and resistant to platidiam and carboplatin in doses ranging from 0.1 to 3.0 TED (Table 1). At doses equivalent to 0.1 TED 72.2±10.6% of tumors were resistant to both platidiam and carboplatin. As the doses increased, the share of tumors resistant to both agents decreased to just individual cases, while the share of tumors resistant to both platidiam and carboplatin increased from 0% at 0.1 TED to 57.1±12% at 3.0 TED. In parallel with this, the share of tumors resistant to platidiam but sensitive to carboplatin increased: at doses higher than 1.5 TED it was at least 33.3±10.3%. By contrast, cases of resistance to carboplatin and sensitivity to platidiam were very few at all doses except 1.0 TED (Table 1).

Hence, the data indicate a somewhat higher mean efficacy of carboplatin in comparison with platidiam vis-a-vis human ovarian cancer cells in the dose range corresponding to 0.1-3.0 TED in the sample studied. In a large proportion of cases the efficacy of carboplatin increases more rapidly than that of platidiam as the dose increases. These findings should be borne in mind when planning chemotherapy for patients with ovarian cancer.

REFERENCES

1. V. A. Gorbunova, *Vopr. Onkol.*, **35**, № 3, 325-330 (1989).
2. V. A. Gorbunova, N. I. Perevodchikova, V. P. Kozachenko, *et al., Akush. Gin.*, № 2, 54-57 (1991).
3. O. A. Kurilyak, *Eksp. Onkol.*, **15**, № 12, 72-77 (1993).
4. S. Inoue, S. Mizuno, and O. Nakajima, *Anticancer Drug Des.*, **6**, № 4, 307-308 (1991).
5. W. Kraff, *Zentralbl. Gynakol.*, **111**, № 14, 938-946 (1989).
6. M. R. Muller, K. A. Wright, and P. R. Twentyman, *Cancer Chemother. Pharmacol.*, **28**, № 4, 273-276 (1991).
7. R. Ozols, *Semin. Surg. Oncol.*, **6**, № 6, 328-338 (1990).
8. J. E. Schurig, A. R. Crosswell, P. A. Trail, *et al., Anticancer Drug. Des.*, **6**, № 4, 277 (1991).
9. J. H. M., Schwachofer, R. P. M. Crooijmans, A. J. Hoogenhout, *et al., Anticancer Res.*, **10**, № 3, 805-812 (1990).
10. P. R. Twentyman, K. A. Wright, P. Mistry, *et al., Cancer Res.*, **52**, № 20, 5674-5680 (1992).