During the first 5-10 min after the end of EAS the duration of the R–R interval of the ECG in response to testing EDS remained the same as at the 20th minute of application of EAS (Fig. 2b, c, 6-7). By the 10th-15th minute after the end of EAS, shortening of the R–R interval of the ECG on average to 230-240 msec began to appear in response to EDS (Fig. 2b, c, 7-8). By about the 20th-25th minute after the end of EAS the R–R interval of the ECG returned more or less to its initial value in response to EDS (Fig. 2b, c, 9).

Electrical stimulation of other nonacupuncture points of the animal's hind limbs, incidentally, did not give rise to the changes in the EEG and EP of the sensomotor cortex described above in response to EDS, and as a rule under these circumstances tachycardia was observed.

Consequently, during EAS gradual disappearance of the response to tachycardia to EDS is observed and after the end of EAS the response is gradually restored.

The results of these experiments thus showed that EAS cause disappearance of the secondary positive wave of the sensomotor cortical EP in rabbits, inhibits the response of tachycardia, and under superficial urethane anesthesia, causes disappearance of the EEG-desynchronization reaction in response to EDS. These observations point to the development of a state of analgesia in the animals. Characteristically the changes in these functions gradually increase during the course of EAS, but after its end gradual recovery takes place, in agreement with the results of clinical observations and of experiments on animals [2, 5]. The study of changes in indices of CNS function such as EP and the EEG in animals can evidently be used for the evaluation of acupuncture analgesia and for the study of its neurophysiological mechanisms.

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THE USE OF HETEROGRAFTS IN DIFFUSION CHAMBERS TO STUDY INDIVIDUAL DRUG SENSITIVITY OF HUMAN OVARIAN CARCINOMA TO CHEMOTHERAPEUTIC AGENTS

I. L. Sobol' and A. F. Marenich

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Experiments with heterografts of human ovarian carcinoma (10 patients) in diffusion chambers revealed considerable individual differences in their sensitivity to chemotherapeutic agents. In four of five cases in which it was possible to compare the experimental results with the results of treatment of the patients with the same agents, correlation was found between the experimental and clinical findings.

KEY WORDS: heterotransplantation; ovarian carcinoma; chemotherapy.

Among the many experimental models which can be used to study the treatment of malignant tumors, the use of heterografts of human tumors in diffusion chambers is particularly interesting. By contrast with the method of culture of human tumors in vitro, in this method various forms of interaction are maintained between the tumor under investigation and the living organism, and the action of therapeutic substances on the tumor can be tested indirectly through the host animal. The use of heterografts in diffusion chambers for the study of individual sensitivity of tumors in particular patients to therapeutic agents is of special interest.

Group for Combined Methods of Treatment and Department of Chemotherapy, Oncologic Scientific Center, Academy of Medical Sciences of the USSR, Moscow.

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TABLE 1. Effect of Chemotherapeutic Agents on Growth of Tumor Transplants

Donor of tumor	Histological characteristics of neoplasm	Therapeutic preparation	Sessional (daily) dose, mg/kg	Number of injections	Results of experiments
D-a	Solid adenocarcinoma	Hexamethylmelamine	75	5	Short-lasting effect
		Cyclophosphamide	75	5	
		5-Fluorouracil	150	1	
		Methotrexate	21	1	
K-r	Papillary adenocarcinoma	The same substances	The same doses	Same number of injections	Effect present
S-a	Papillary adenocarcinoma	The same substances	The same doses	Same number of injections	No effect present
K-a	Serous papillary adenocarcinoma	Hexamethylmelamine	50	5	No effect present
		Cyclophosphamide	50	5	
		5-Fluorouracil	100	1	
		Methotrexate	14	1	
A-a	Serous papillary cystadenocarcinoma	The same substances	The same doses	Same number of injections	No effect present
A-a	Mucous carcinoma	Hexamethylmelamine	75	5	Effect present
		Cyclophosphamide	75	5	
		5-Fluorouracil	150	1	
			0.15	1	
		17-hydroxyprogesterone capronate	1 mg per mouse	2	
S-o	Papillary cystadenocarcinoma	The same substances	The same doses	Same number of injections	No effect present
As-a	Papillary adenocarcinoma	Cyclophosphamide	60	2	No effect present
		5-Fluorouracil	25	1	
E-a	Mucinous cystadenocarcinoma	The same substances	The same doses	Same number of injections	No effect present
I-a	Papillary carcinoma	Thio-TEPA	2	5	Effect present

Legend. Hexamethylmelamine was given per os, cyclophosphamide per os or intraperitoneally, methotrexate, 5-fluorouracil, actinomycin D, and thio-TEPA intraperitoneally, and 17-hydroxyprogesterone capronate subcutaneously.

In the accessible literature we found only three publications in which the authors had studied the sensitivity of ovarian tumors to chemotherapeutic agents. Heckmann et al. [2, 3] found considerable individual differences in the sensitivity of these tumors to various chemotherapeutic agents. According to Limburg [4], selection of therapeutic substances for the treatment of ovarian tumors, based on determination of individual sensitivity of heterografts of the tumors to the corresponding agents, leads to a marked increase in the efficacy of chemotherapy of these tumors.

The object of the present investigation was to study the effect of chemotherapeutic agents on heterografts of human ovarian carcinoma and to compare the results of these experiments with those of treatment of patients with the same agents.

EXPERIMENTAL METHODS

Tumor tissue for heterografting was obtained from the operating theater of the Department of Gynecology at the Clinic of the Oncologic Scientific Center, Academy of Medical Sciences of the USSR. The method of heterografting described previously [1] was used. Some of the experiments were performed on (CBA × C57BL)F_1 mice, some on noninbred mice. The animals with heterografts were divided into two groups: The animals of one group (experimental) received the chemotherapeutic agents, whereas those of the other group (control) received intraperitoneal injections of pyrogen-free physiological saline. Injections both of therapeutic agents and of physiological saline began 1-5 days after transplantation of the tumor, when microscopic examination revealed the first signs of commencing proliferation of the cells of the graft. The results of chemotherapy

were assessed qualitatively on the basis of comparison of the pictures found on microscopic investigation of the grafts from the experimental and control animals.

EXPERIMENTAL RESULTS

As the results in Table 1 show, administration of hexamethylmelamine, cyclophosphamide, 5-fluorouracil, and methotrexate in a combination led to delayed growth of the grafts in two of five experiments, and in one of them (patient D-a) the effect was short-lasting: Three days after the end of treatment delayed growth of the grafts in the experimental animals was observed, but after six days no difference could be found between the two groups. In another experiment (patient K-r), both two days and seven days after the end of the therapeutic course, growth of the tumor cells was completely suppressed in the experimental animals. When a combination of hexamethylmelamine, cyclophosphamide, 5-fluorouracil, actinomycin D, and 17-hydroxyprogesterone capronate was used, delayed growth of the grafts was observed three and five days after the end of treatment in one of the two experiments. In two experiments in which cyclophosphamide was used in combination with 5-fluorouracil, no difference was found five and ten days after the therapeutic course between the pattern of growth of the heterografts in the experimental and control animals. In the experiment with thio-TEPA considerable delay of growth of the grafts was observed in the experimental animals compared with the controls.

Comparison of the results of the five experiments with the results of treatment of the corresponding patients with the same preparations revealed correlation in four of the five cases. In one (patient K-r) a reduction in size of the tumor by more than 50% and disappearance of the ascites were observed after chemotherapy, and in the corresponding experiment a definite therapeutic effect also was obtained. In another case (patient D-a) a very slight temporary effect was observed, and in the corresponding experiment only temporary inhibition of growth of the heterografts took place. In two patients (As-a, S-a) chemotherapy was ineffective, and in the corresponding experiments growth of the heterografts likewise was not inhibited. Disagreement between the results was observed in one case (patient K-a), when no changes in growth of the heterografts were observed in the experimental animals compared with the controls, whereas the tumor in the patient was reduced in size by more than 50% after chemotherapy and the ascites disappeared. In the other two patients (E-a, I-a) it was too early to compare the experimental results with the clinical findings and a longer period of observation on the patients was necessary.

In four of five cases correlation was thus found between the experimental results and the course of the disease in the patients after chemotherapy.

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