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ADSORPTIVE THERAPY AS A MODIFICATOR FOR TUMOR-HOST INTERACTION

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The potential of one of the adsorption methods, enterosorption (ES), using the new generation of carbon adsorbents to correct the negative manifestations of tumor-host interaction in the framework of paraneoplastic syndrome (PNS) as well as systemic toxicity of chemo- and radiation therapy, is discussed. The ES influence on the development of PNS was demonstrated in C57/BL6 mice with transplanted Lewis lung carcinoma. Two-week administration of carbon enterosorbents resulted in a significant suppression of metastasis and correction of tumor-related anemia, activation of granulocytic line in the bone marrow with nearly 3-fold enhancement of its mitotic activity. ES exerted a positive influence on the structural-morphologic indexes and regenerative potential of kidneys and liver, mitigated manifestations of oxidative stress, decreased the level of endogenous intoxication, increased resistance of erythrocyte membranes and decreased ligand loading of blood plasma transport proteins. The effect of ES on anticancer activity and toxic reactions of cisplatin (CP) was evaluated in Guerin carcinoma-bearing rats. ES reduced significantly creatinine and other kidney biochemical indexes elevated in the blood plasma of rats after CP treatment. ES attenuated dystrophic changes in the histological structure of internal organs (kidney, liver, spleen), caused by tumor growth and significantly aggravated under the influence of CP. Such changes were specially traced in the kidneys and well reflect the nephroprotective potential of ES. In rats irradiated with X-ray in sublethal dose, highly activated granulated carbonic enterosorbents facilitated the restoration of white blood cells and lymphocyte count. The results obtained confirm the insights of academician R.E. Kavetsky predicting the future of adsorptive detoxification with activated carbons in the treatment of cancer patients.

***Key Words*: enterosorption, hemosorption, HemoSorbent Granulated Deliganding, paraneoplastic syndrome, radio- and chemotherapy, cisplatin.**

The brilliant idea of the interaction between tumor and host has actually defined the development of the new area of cancer research dealing with the systemic manifestations of a neoplastic disease. One of the principal questions considered in the monograph of academician R.E. Kavetsky is the ability to normalize the tumor-host relations by affecting not only the tumor cells but also the organism as a whole [1]. In this connection, the author has foreseen the indisputable prospects for using the systemic methods of organism detoxification in oncology and, in particular, the method of hemosorption (HS) with the activated carbons. As shown in the 70s of the last century, this method could ensure the removal of toxic products generated both in the process of tumor growth and as a result of the treatment. HS was supposed to be especially demanded in the complex of intensive treatment of malignant neoplasms.

Today, a significant role in solving the problem of reducing the systemic toxicity is given to modern sorption technologies based on powerful sorbents for medical use. The use of HemoSorbents Granular Deliganding (HSGD) developed in R.E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology of the NAS of Ukraine for the effective removal of hydrophobic toxic metabolites, strongly associated with plasma proteins, allows to obtain qualitatively new therapeutic effects related to deep purification of transport proteins and blood cell membranes in patients with myocarditis, hepatitis and renal failure caused by cytostatic therapy [2, 3]. Likewise, HS method, according to Kavetsky and Nikolaev, opened up unique opportunities for managing the pharmacokinetics of anticancer drugs [4]. The technique of regional administration of high doses of anticancer drugs with subsequent adsorptive purification of the blood flow creates therapeutically significant differences between the concentration of cytostatics in the tumor and in the most vulnerable organs. Extracorporeal module on the base of highly active HSGD is capable in such case to provide a powerful sorption barrier that limits the entry of antitumor drugs into the systemic circulation. This opens up real prospects for using the high doses of cytostatics without the risk of systemic toxic effects.

Chemo- and radiation therapy side effects seem to be interpreted as a peculiar manifestation of tumor-host interactions in the setting of external toxic influence. The patterns of such interactions may be modified be therapeutic systemic methods such are sorption ones. And “The possibility is not excluded that just such systemic treatments could be the main components of future tumor radical therapy schemes”, — with these words academician R.E. Kavetsky ends his monograph “Host and Tumor Interaction”.

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Abbreviations used: CP – cisplatin; ES – enterosorption; HS – hemosorption; HSGD – HemoSorbent Granulated Deliganding; LLC – Lewis lung carcinoma; PNS – paraneoplastic syndrome.

The range of tasks that sorption therapy can solve is constantly expanding due to the creation of new sorption means and methods for their use [5]. One of these is the method of enterosorption (ES) allowing today to effectively deal with exogenous and endogenous intoxications of various origins, and wherein being simple for mass use.

ES FOR CORRECTING MANIFESTATIONS OF PARANEOPLASTIC SYNDROME

One of the most demonstrative aspects of the tumor-host interaction is the paraneoplastic syndrome (PNS), which covers significant metabolic disorders, the immune conflict between the tumor and the host, complex changes in the structure and functions of many organs and systems. The fact that carbon enterosorbents possess a number of properties that make them capable to normalize cytokine profile, endothelial dysfunction and some immunological parameters, to mitigate the manifestation of myelosupression, to elevate functional activity of detoxification systems and to improve their morphological parameters and regenerative potency [6] allowed us to consider ES as an effective method to correct some paraneoplastic symptoms.

The ability of ES to influence some manifestations of PNS was studied in male C57/BL6 mice with transplanted Lewis lung carcinoma (LLC). Fine carbon fraction of HSGD ($\gamma = 0,155$ g/cm^3) was administered daily at a dose of 0.625 g/kg for two weeks starting from the 7th day after tumor cell transplantation. Such fine carbon fraction (average particle size is ≈ 2 μ) was used because of large external surface area and high kinetic of adsorption which was evaluated by adsorption of marker compounds [7]. Despite high adsorption activity, powder enterosorbent was found to be absolutely nonaggressive for gastrointestinal mucosa [8]. Morphologic examination of gastric fundus, small intestine, and large bowel slides after 2-week ES evidenced high safety and proper evacuation of enterosorbent from an organism of experimental animals.

The administration of enterosorbents resulted in significant metastasis suppression, namely, nearly 2-fold decrease of metastases number and correction of tumor-related anemia and thrombocytopenia. So, the number of red blood cells and the level of hemoglobin were higher by 30.0% ($p < 0.05$) and 23.3% ($p < 0.05$), respectively in enterosorbent-treated mice in comparing with control group of LLC-bearing animals. ES prevented the development of thrombocytopenia: platelet counts in tumor-bearing mice were at the level of intact animals and significantly higher than in untreated animals of negative control group. Activation of granulocytic lineage of hematopoiesis along with significant increase of mitotic cell counts (6.5-fold and 4.3-fold, respectively) took place, wherein the number of mitoses in erythroid lineage cells tended to decrease. In contrary, erythrocyte counts in peripheral blood of animals in ES group increased. Such facts demonstrate damage of circulating erythrocytes (possibly of autoimmune genesis) as hypothetic mechanism of anemia development in mice with LLC tumors, while ES therapy corrected this effect [9].

ES session normalized the morphological structure of kidneys and liver and improved the functional activity of kidneys in tumor-bearing animals. The concentration of uric acid and creatinine in blood plasma decreased markedly, and the urea content approached the values in the group of intact mice. The content of “middle molecules” in blood plasma (an integral indicator of endogenous intoxication) decreased by 32.5%. After ES, biochemical indices of peripheral blood were indicative of the decrease of endogenous intoxication, the shift of prooxidant-antioxidant balance in favor of the latter, the increased resistance of erythrocyte membranes and decreased ligand loading of blood plasma transport proteins. The latter was confirmed by differential scanning calorimetry that demonstrated the noticeable deliganding of albumin molecule and partial normalization of its “architectonics” [9].

Therefore, the presented data denote that ES therapy can be considered as an advanced treatment of cancer patients directed toward correction of a number of manifestations of paraneoplastic syndrome.

ES FOR TREATMENT OF MYELOSUPPRESSION

Radiation and drug therapy are powerful myelosuppressive factors. The degree of leukopenia undoubtedly correlates with overall survival and clinical outcome in cancer patients [10, 11]. Treatment of leukopenia in clinical protocols includes the use of granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor, transfusion of blood components, antimicrobials support etc., and even hematopoietic stem cell transplantation [12]. Nevertheless, the search for the novel effective agents and methods to protect the bone marrow still remains relevant.

In this regard, it would be appropriate to recall the result obtained in 1976 by our team and the team of Dr. L.B. Pinchuk in an experiment with 69 inbred dogs irradiated with external irradiation at a dose of 5.25 Gy (LD_{90}), which demonstrated a pronounced myeloprotective effect of single hemoperfusion conducted after irradiation to protect the bone marrow [13]. Mitotic index (‰) in the bone marrow of the dogs treated with hemoperfusion (n = 19) was more than 2 and 12 times higher respectively on the 6th and 16th days after irradiation in comparison with non-treated irradiated control and correlated with survival rate of animals (68% in hemoperfusion-treated animals *vs* 3% in control). In our recent experiments with rats irradiated with X-ray at sublethal dose, the use of highly activated granulated charcoal (bulk density 0.12 g/cm^3) accelerated the restoration of white blood cell and lymphocyte level twice in comparison with irradiated control on the 9th day after injury [14].

ES FOR TREATMENT OF SYSTEMIC TOXIC EFFECTS OF CHEMOTHERAPY

Minimizing the systemic toxic effects of chemotherapy without reducing its antitumor activity is one of the most important tasks of clinical oncology. Application of one of the widely used anticancer drugs — cisplatin (CP) is strictly limited due to its toxic effects and, largely, nephrotoxicity. This explains the large number of studies aimed at searching the nephroprotective agents [15, 16]. In this regard, the results of our experimental studies on the effect of ES on antitumor activity and toxic reactions of CP in Guerin carcinoma-bearing rats can be of great interest [17]. CP has been injected every other day at a dose of 1.0 mg/kg bw for two weeks and ES (dispersed fibers of activated carbon-fibrous material) was administered daily at a dose of 0.65 g/kg bw 1 h after CP injection. Three days after the last administration of the preparations (on Day 22 after transplantation) on the background of ES there was a significant reduction in creatinine and other biochemical indexes of the renal as well hepatic profile, elevated in the blood plasma of rats after CP treatment. Loss of the body weight and increase of the relative kidney weight of rats caused by CP decreased by 1.6 and 1.3 times, respectively, in ES-administered rats. The modifying effect of ES on the manifestations of systemic toxicity of CP was convincingly confirmed by a comparative analysis of changes in the histological structure of the internal organs.

ES attenuated dystrophic changes in the histological structure of kidney, liver and spleen, caused by tumor growth and significantly aggravated under the influence of CP. Morphological study of kidney tissues of rats with Guerin carcinoma has revealed the hemorrhages in glomerulus and hyalinosis in renal tubule (Fig. 1, *a*). CP impaired noticeably morphological structure of renal tissue (Fig. 1, *b*) resulting in dystrophic changes in functional cell elements, tubular necrosis, and destruction of the glomeruli with formation of large lumens between the tubules. In kidneys of tumor-bearing rats treated with CP with concomitant ES, only rare hemorrhages in glomeruli were detected while the cellularity increased significantly. The large majority of cells in tubules were of normal morphological structure, the cavities between the tubules became smaller. In some animals, the morphological structure of the kidneys was close to that in healthy rats (Fig. 1, *c*).

ES also affected the morphological structure of Guerin carcinoma (Fig. 2). Instead of large necrotic sites in tumors after CP treatment (Fig. 2, *b*), after CP treatment with concomitant ES we observed the areas of newly formed connective tissue (Fig. 2, *c*). These data and the fact that ES itself caused a slight suppression of the tumor growth and to some extent contributed to the CP inhibitory effect, allow us to conclude that the powerful detoxification effect of carbon enterosorbents is realized under preserving the CP cytostatic activity.

Earlier, we have reported the positive effects of fibrous carbon enterosorbents in the patients with Hodgkin disease undergoing intensive radiotherapy [18]. ES permitted to continue the planned radiotherapy due to leukopenia prevention. ES has a high capacity to reduce the emesis caused by anticancer treatment [19]. It is a unique mean with antidiarrhea action and could be implemented in the clinics. It could be suggested that ES after each session of chemo- or radiation therapy could be effective method to minimize their systemic toxic effects.

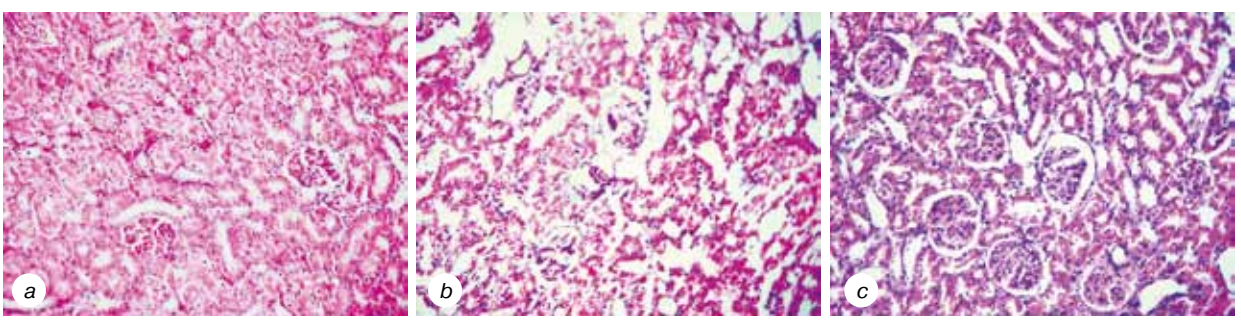

Fig. 1. Microphotographs of kidney: *a* — Guerin carcinoma-bearing rats; *b* — upon CP treatment; *c* — upon CP + ES treatment. Hematoxylin-eosin. ×200

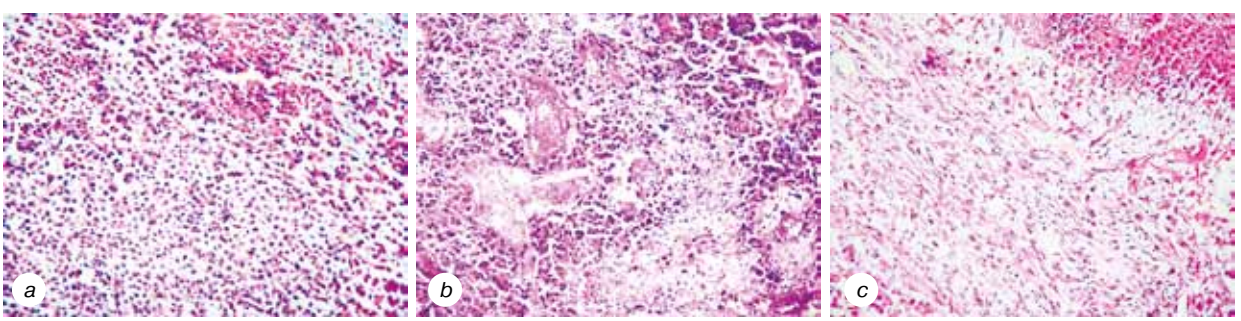

Fig. 2. Microphotographs of Guerin carcinoma on Day 22; *a* — intact; *b* — upon CP treatment; *c* — upon CP + ES treatment. Hematoxylin-eosin. ×200

Our experimental results and some clinical observations convincingly prove the correctness of academician R.E. Kavetsky, who foresaw the role of adsorption detoxification with activated carbons in the treatment of cancer patients. Negative manifestations of tumor-host interaction in the framework of paraneoplastic syndrome as well as of systemic toxicity of chemo- and radiation therapy, could be significantly corrected with a help of a new generation of carbon enterosorbents.

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