Exp Oncol 2013
35, 1, 45–52

Experimental ONCOLOGY

ENTEROSORPTION AS A METHOD TO DECREASE THE SYSTEMIC TOXICITY OF CISPLATIN

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A perspective adsorptive method to minimize systemic toxic effects of chemotherapy is enterosorption (ES). However, the capabilities of this method are far from being completely studied. The question remains opened — should ES be initiated in the first hours on completing cytostatic infusion without the risk of their anticancer activity to be decreased. *Aim:* to analyze ES influence on anticancer activity and toxic reactions of cisplatin (CP) upon the use of carbon enterosorbent in 1 h after intravenous administration of cytostatic. *Methods:* CP at the dose of 1 mg/kg body weigh (BW) was administered to Guerin carcinoma-bearing rats each second day for two weeks. Enterosorbents on the basis of highly activated carbon fibers were administered by per os daily 1 h after CP injection. 3 days after the last CP administration the rats were weighted and blood under ether narcosis has been taken for biochemical examination. Tumors and innate organs were isolated, weighted, and fixed in 4% buffered formalin for morphologic examination. *Results:* In rats administered with CP at the background of ES, BW loss was in 1.6 times lower than in animals after CP session. Relative kidney weight in CP-treated rats was 33.9% higher than in normal ones ($p \leqslant 0.05$). No significant differences were detected between relative kidney weights in the CP + ES-treated and intact animals. Introduction of ES allowed prevent an 30% increase of creatinin content observed in blood plasma after CP treatment ($p \leqslant 0.05$). Urea content was 1.7 times lower in blood plasma of CP + ES-treated rats than after CP treatment. CP caused significant toxic injuries in kidneys, liver, and spleen tissues. Morphologic structure of organs in rats treated with CP at the background of ES was affected at much lower degree. In tumors, large areas of newly formed connective tissue and blood vessels have been fixed after the CP+ES action instead of large necrotic area observed after CP treatment. ES caused insignificant suppression of Guerin carcinoma growth and had additional impact to inhibitory action of CP. *Conclusion:* Active carbon enterosorbents which are administrated just 1 h after CP administration possesses detoxicating potential sufficient for significant elimination of toxic effect of the cytostatic at the background of complete preservation of its antitumor activity.

***Key Words*: enterosorption, activated carbon fibrous sorbents, cisplatin, chemotherapy.**

The search for way to minimize systemic toxic effects of chemotherapy without the decrease of its anticancer activity is still actual. A special place in this problem solving is occupied by the methods of sorption therapy the possibilities of which are being constantly expanded due to the development of new effective sorbents of medicinal purposes and original approaches for their use.

After massive chemotherapy accompanied with an expressed endogenous intoxication syndrome and cytostatic-dependent myelodepression, the method of hemosorption (HS) allows significantly alleviate these complications and thereby provide the possibility to continue the therapy by radical schemes [1]. In such situations the use of Hemosorbents Granulated Deliganding (HSGD) developed in R.E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology of NAS of Ukraine (IEPOR) for effective removal of hydrophobic toxic metabolites strongly bound with blood plasma proteins (nonconjugated bilirubin, free fatty acids, phenols, bile acids, mercaptanes, a number of uraemic toxins) during HS procedure allows achieve 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].

HS method provides unique possibilities for control of local and systemic pharmacokinetics of anticancer preparations. Therapeutically significant differences between the concentrations of anticancer preparations in the tumor and the most vulnerable organs are achieved in the first variant via selective intraarterial administration of high doses of cytostatics with the following sorption purification of blood which outflows from an affected organ [4–7].

Sorption system on the basis of highly active hemosorbents of HSGD type performs deep blood purification from protein bound compounds including the large majority of anticancer preparations, and is capable to provide a safe sorption barrier that limits anticancer agent entering into systemic circulation. Thus, such approach allows regional introduction of high doses of cytostatics into the tumor with the decreased risk of systemic toxic effects. To increase the efficacy of removal from blood of cisplatin (CP) excess during the control of its local pharmacokinetics, one would sequentially introduce sorption column and dialyzator into extracorporeal circuit [8]. The other method proposed is related to the control of systemic pharmacokinetics and make unneedful the collection of blood enriched with chemopreparation excess directly from

Received: February 8, 2013.
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Abbreviations used: ACFS – activated carbon fibrous sorbents; CP – cisplatin; ES – enterosorption; HS – hemosorption; HSGD – Hemosorbent Granulated Deliganding; BW – body weight.

venous collectors of separate organ or tumor lesion, into which intraarterial catheter for cytostatic administration is applied. Instead of this blood is taken with high speed (from 500 ml/min to 1 ml/min and more) from any appropriate vasculature point and is returned into systemic circulation after massive sorption purification providing removal not less than 95% of chemopreparation. This variant also allows provide effective defence of vital organs from the action of high doses of cytostatic drugs [9]. One should mention that local scheme as well could provide the control of systemic pharmacokinetics of anticancer preparation, however just in a case when its concentration on column entry is lower that systemic concentration supported by incomplete isolation of regional circle. In both mentioned cases the action of HS is not limited by its effect on the local and systemic concentration of anticancer drugs the large majority of which are related to radiomimetics, i.e., chemical compounds simulating the action of penetrating radiation. That's why it is reasonable to mention our previous results on the use of hemocarboperfusion method in a treatment of acute radiation sickness; then blood purification in dogs at the terms of 2 to 24 h after their homogenous irradiation at minimal absolutely lethal dose of 5.25 Gy has allowed achieve 65–70% animal survival at the background of an expressed myeloprotective effect [10]. It could not be excluded that such effect of HS could be true also for cytostatic therapy as far as for anticancer cytostatic pharmacokinetic control, but sorption purification of blood is performed not after accomplished radiation injury as in a case of early treatment of acute radiation sickness, but strictly during the primary action of radiomimetic agent.

As a perspective method to fight endotoxicosis caused by systemic toxicity of anticancer cytostatics, one could consider enterosorption (ES), which efficacy has been initially proven by the results of experimental studies with the use of animals bearing transplanted tumors [11–13].

In the frame of study of ES effect toward myelotoxicity of anticancer preparations, there have been shown that ES performed in Guerin carcinoma-bearing rats after treatment with cyclophosphamide and methotrexate, has demonstrated an expressed myeloprotective effect toward all main bone marrow cell elements [13]. In Shvets erythromyelosis-bearing rats treated with carminomycine the myelocaryocyte and peripheral granulocyte counts were two and three times lower, respectively, that these in animals that were treated with carbon enterosorbents after antibiotic treatment [13]. Along with this ES alone demonstrates insignificant suppressing effect toward transplanted tumor growth and elongates life time of animals treated with cytostatics compared to animals which are not treated with ES. In patients with Hodgkin's lymphoma two-week ES course after intense chemoradiotherapy allowed reduce leukopenia duration by 1.5 times [14].

ES efficacy has been successfully applied in patients with malignant breast tumors and large bowel cancer at the post-operative period [15]. Two-weeks administration of carbon-mineral sorbent SCMS-1 with immobilized metronidazole which has been initiated a day after beginning of chemotherapy course, prevented the development of expressed leukopenia and thrombocytopenia, elevation of urea and bilirubin contents, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels in blood plasma, and also decreased an intensity of clinical intoxication symptoms — nausea and vomiting.

An important step in ES development was done by creation of moist boluses or granules formed from carbon fibers or micronized carbon particles with the use of water as a binder (Carboline, IEPOR production, Ukraine). Such technology provides total preservation of adsorptive properties of the sorbent and improves the kinetic parameters of adsorption. Also, the washed down preparation is immediately dispersed in oral cavity and is swallowed easily what is of special importance in the patients with increased vomiting activity. An efficacy of the use of carbon enterosorbent Carboline for prophylaxis of acute and delayed emetogenic toxicity of cytostatics has been demonstrated in patients with breast and lung cancer and Hodgkin's disease [16]. Carboline at the dose of 15 tablets daily for 5 days before and 5 days after polychemotherapy session (ES is not indicated at the day of cytostatic administration) allows prevent severe toxic reactions caused by polychemotherapy which includes platinum group preparations, and by 4 times increases the number of patients without toxic reaction caused by platinate-free polychemotherapy. Delayed emetogenic toxicity characteristic nearly for half of the patients, has been observed just in 5% of the patients treated with ES.

So, the results of experimental studies and the data of clinical observations support an expediency of ES introduction into the complex of measures directed on prophylaxis and minimization of systemic toxic effects of anticancer preparations. However, the capabilities of this method are far from being completely studied yet. In particular, the question remains — should ES be initiated in the first hours on completing cytostatic perfusion without the risk of decreasing the anticancer activity of the preparation. Therefore, the task of our experimental studies was to analyze ES influence on anticancer activity of CP and toxic reactions upon the use of carbon enterosorbent in 1 h after intravenous administration of cytostatic characterized by quick clearance from blood via glomerular excretion [17]. According to our earlier results (unpublished data), CP concentration in blood serum of Guerin carcinoma-bearing rats 5 min after intravenous administration of CP was equal to 24.5% of injected dose and was not higher than 3 and 0.9% in 1 and 24 h respectively. Such pharmacokinetics of the cytostatic has been described for athymic mice bearing subcutaneous A2780 cell ovarian xenografts [18].

MATERIALS AND METHODS

Animals and experimental design. The studies were carried out on white inbred rats weighting

200 ± 20 g from the IEPOR vivarium. All animals procedures were carried out according to the rules and requirements of local Ethic Committee of IEPOR. Guerin carcinoma T8 was transplanted subcutaneously in the left femur of animals. When tumor volume reached approximately 0.5 cm^3 animals were randomly distributed according to their tumor volume into 4 groups: 1 — intact Guerin carcinoma-bearing rats (*tumor)* (n = 7); 2 — Guerin carcinoma-bearing rats treated with ES (*tumor + ES)* (n = 8); 3 — with CP (*tumor + CP)* (n = 8); and 4 — with CP and ES (*tumor + CP + ES)* (n = 8). Control group consisted of 6 normal rats.

CP (Veropharm, Russia) has been injected each alternate day in tail vein at the dose of 1.0 mg/1 kg body weight (BW) for 2 weeks.

As enterosorbent, Carboline on the basis of highly activated fibrous carbon materials (Ukraine) was used. The fibers at the quantity of 0.65 g/1 kg BW as a suspension in 2 ml of distilled water were introduced with the use of tube into rat stomach 1 h after CP administration. Rats treated with CP only were introduced with 2 ml of distilled water without the sorbent. Animals treated with enterosorbents received 0.5 ml of physiologic solution instead of CP.

Tumor volume was determined by three orthogonal diameters (a, b, c) according to the prolate ellipsoid formula: V = 0.52 (a×b×c). To characterize the dynamic tumor growth we have used K coefficient determined as the ratio between tumor volume at the given moment and tumor volume at the moment of the first CP injection.

Three days after the last administration of the preparations the rats were weighted and blood under ether narcosis has been taken from *vena cava inferior*. Tumors and innate organs (lever, kidney, spleens) were isolated, washed with cold physiologic solution, weighted, and fixed in 4% buffered formalin.

The loss of BW was calculated using the following formula: BW loss (%) = (BW at the 1st day of CP injection — BW at the 3rd day after last CP injection) x100/ BW at the first day of CP injection.

Plasma concentrations of creatinin, urea, urinary acid, AST and ALT were analyzed at the clinical laboratory using a Clinical System (Beckman, CA).

The statistical significance of the differences between mean values was assessed by the Student's *t*-test.

Morphology examination. Fixed in formalin tissues of organs and tumors were sectioned, dehydrated in 70% ethanol and paraffin embedded according to routine technique. Serial 5 μm sections were stained with hematoxylin and eosin, examined by light microscopy.

RESULTS AND DISCUSSION

The main task of our study was to analyze ES effects toward systemic toxic CP reactions in Guerin carcinoma beagin rats treated with enterosorbent 1 h after intravenous administration of the cytostatic.

The decrease of animal BW could serve as an indicative criterion of endotoxicosis caused by toxic effects of the cytostatic and in part — by tumor growth [19]. Before CP administration, the Guerin carcinoma-bearing rat BW was recorded. No significant differences were detected between the intact tumor, tumor+ES, tumor+CP, tumor+CP+ES groups: 249.8±22.4; 246.2±19.4; 254.4±19.0; 242.6±14.1 g respectively. In the process of tumor development animal BW in intact tumor group decreased by 9.4±4.1% versus 7.4±3.6% in tumor+ES group (Table 1). After CP session the animal BW loss was 13.1±8.7%. Introduction of ES allowed decrease BW loss by 1.6 times. In tumour-bearing animals there has been recorded insignificant elevation of relative kidney weight (total organ weight/BW) while in rats treated with CP this index was 33.9% ($p \leqslant 0.05$) higher than in normal animals. In rats treated with CP+ES relative kidney weight didn't differ significantly from respective value in control group. An increase of relative kidney weight by 1.5 times along with alterations in some biochemical indexes and glomerular and tubular disruption has been observed in Guerin carcinoma-bearing rats upon single intraperitoneal administration of CP at the dose of 8 mg/kg [20]. Kidney hypertrophy is among manifestations of compensatory reaction in response to nephrotoxic agent action and is caused by adaptive increase of the size of remaining functional nephrones in which filtration rate and reabsorption of water-soluble compounds is being increased [21].

Table 1. Influence of ES on toxic reactions caused by Guerin carcinoma growth and cisplatin administration

Index	Groups				
	Normal rats	Guerin carcinoma-bearing rats			
		Intact	ES	CP	CP + ES
BW loss, %		9.4±4.1	7.4±3.6	13.1±8.7	8.3±3.7
Kidney weight/BW	6.2±1.3	6.8±0.8	6.3±0.7	8.3±1.7*	7.8±1.0
Liver weight /BW	44,0±5.1	51.2±8.2	44.5±6.3	48.7±3.1	43.8±6.2
Spleen weight/BW	5.8±1.0	9.5±2.9	9.3±1.7	5.0±0.9	4.2±0.7
Blood plasma creatinin content, mMol/l	61.9±5.7	71.0±9.7	58.4±11	80.3±9.0*	67.7±9.2
Blood plasma uric acid content, mMol/l	118±17.8	114±15.6	122±10.4	102±11.9	85±7.9
Blood plasma urea content, mMol/l	8.9±1.1	9.3±0.9	10.4±1.2	11.7±1.6	10.5±1.2
Blood plasma ALT, U/l	65±17	64±11	61±9	76±13	59±11
Blood plasma AST, U/l	135±19	-	-	212±16*	143±18

* Difference is significant compared to the normal rats ($p \leqslant 0.050$).

After CP treatment insignificant increase of relative weights of liver and spleen in tumor + CP and tumor + CP + ES groups has been registered (Table 1), and more expressed one — in intact Guerin carcinoma-bearing rats. ES has been causing normalizing effect on relative liver weight, but had no effect on spleen hyperplasia (tumor + ES group).

Blood plasma level of creatinin is a standard marker of glomerular disruption [20, 21]. Creatinin content which was practically equal in blood plasma of tumor-bearing rats and intact animals, has been elevated by 30% after CP session ($p \leqslant 0.05$). Introduction of ES allowed prevent an increase of this index. After CP session there has been registered an elevation of urea content in blood plasma by 31%, while after combined treatment with CP + ES — by 17.9%. Uric acid content in blood plasma of rats from these groups stood within values of intact animals. AST level in rats treated

with CP was higher by 1.4 fold, and in animals treated with CP+ES was equal to that in intact control. No significant differences in ALT levels have been recorded.

The observed tendencies evidencing on modifying effect of ES on systemic CP toxicity, have found new confirmation during comparative analysis of alterations of histological structure of innate organs of rats upon tumour growth and CP or CP + ES treatment.

Morphological study of liver tissues of Guerin carcinoma-bearing rats has revealed the disruption of beam structure and dystrophy of hepatocytes, increased number of Kupffer cells and their sizes, and the presence of phagocytized cell debris in their cytoplasm (Fig. 1 *a*). Enlargement of sinusoids and accumulation of erythrocytes inside them could evidence on toxic effect of growing tumor on cell membranes of hepatocytes and endothelial cells. In kidney tissue there has been observed an expressed tubular cell dystrophy, formation of lumen and decreased cell element numbers in glomerulus which in some glomerulus are represented just by 'naked' nuclei (Fig. 1 *b*). In the majority of glomerulus one could observe haemorrhages of various degree, in tubular lumen — small lesions of haemorrhages and hyaline inclusions. Morphological structure of spleen was characterized by increased number of lymphoid follicles, some of them contained secondary germinal centers with blast elements, and rarely — significant amounts of macrophages (Fig. 1 *c*).

At the background of ES the morphological changes in innate organ structure caused by growing tumour have been expressed at significantly lower level (Figc. 2 *a–c*). In some animals the morphological picture was close to normal one.

Upon CP action the degree of toxic damage of innate organ tissues drastically decreased. Morphologic structure of liver tissue is notably disrupted, large necrosis area could be noticed. Hepatocytes are mostly in necrobiosis state. The rest of them have patterns of dystrophy (Fig. 3 *a*). Also, in liver cells there were observed "naked" nuclei, cell shadows, and empty cytoplasm. One could see small haemorrhages between hepatocyte cords and hyalinization of some vessels. CP caused notable disruption in renal tissue structure, alteration of anatomic region of glomerulus location which contained lower numbers of functional cells (Fig. 3 *b*). There have been recorded dystrophic changes practically in all functional cell elements, tubular necrosis, destruction of glomerules and formation of large lumens between tubules. In spleen tissue there was observed the formation of large secondary germinal centers, devastation of cells in marginal zone of spleen, erythrocyte destruction in red pulpa with appearance of small haemorrhages (Fig. 3 *c*).

Microscopic picture of innate organ tissues of rats treated with CP and carbon enterosorbents is completely different: their morphological structure is affected at significantly lower degree however, it varies between some animals (Fig. 4 *a–c*).

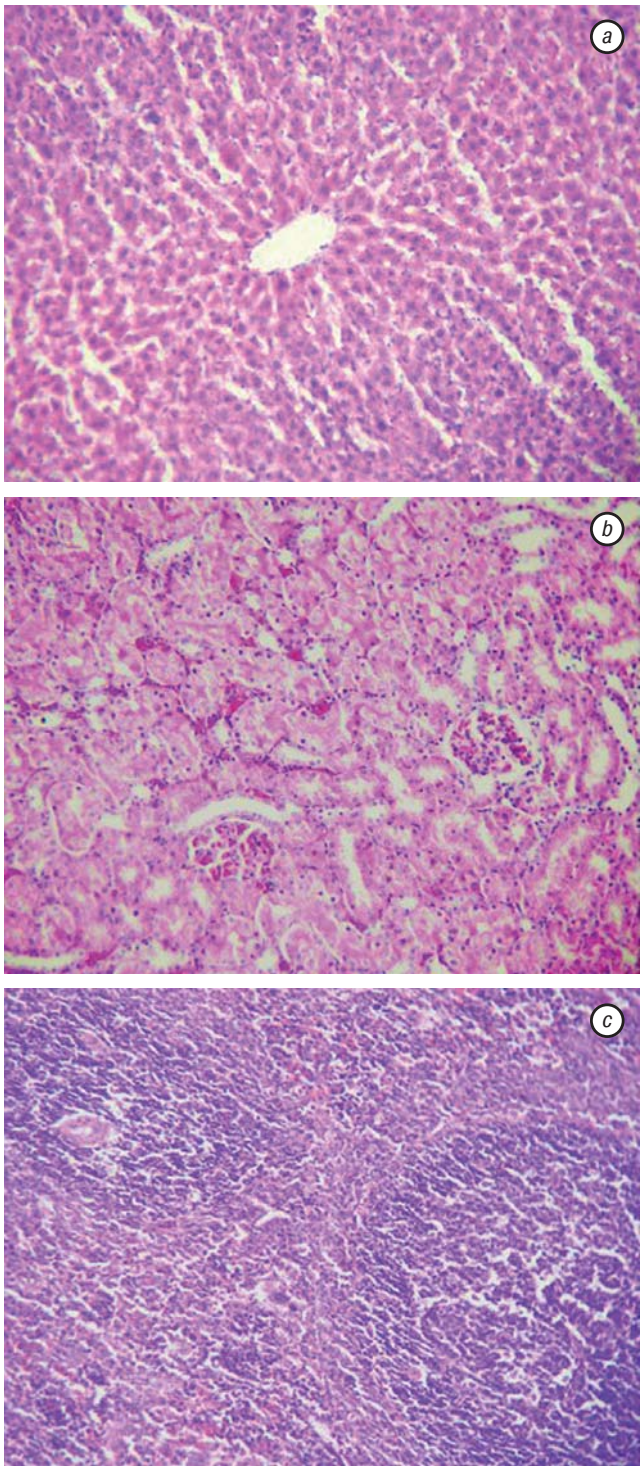

Fig. 1. Morphological structure of innate organs in Guerin carcinoma-bearing rats (x 200): *a* — disruption of beam structure and dystrophy of hepatocytes in liver; *b* — haemorrhages in glomerules and hyalinosis in renal tubules; *c* — secondary germinal centers with blast elements in spleen

In one rat liver structure is completely normal. In other animals hepatocytes possessed the patterns of dystrophy of different degree. However, in this cases around vessels there has been detected an appearance of hepatocytes possessing more basophilic cytoplasm and dense nucleus (so called dark hepatocytes) which represent young liver cells that replace dead ones; this fact points on improvement of functional state of liver. In kidney tissues toxic disruption is expressed at lower level. There were no erythrocytes and haemorrhages in glomerules, and high cellularity has been registered. In tubular lumen there was detected

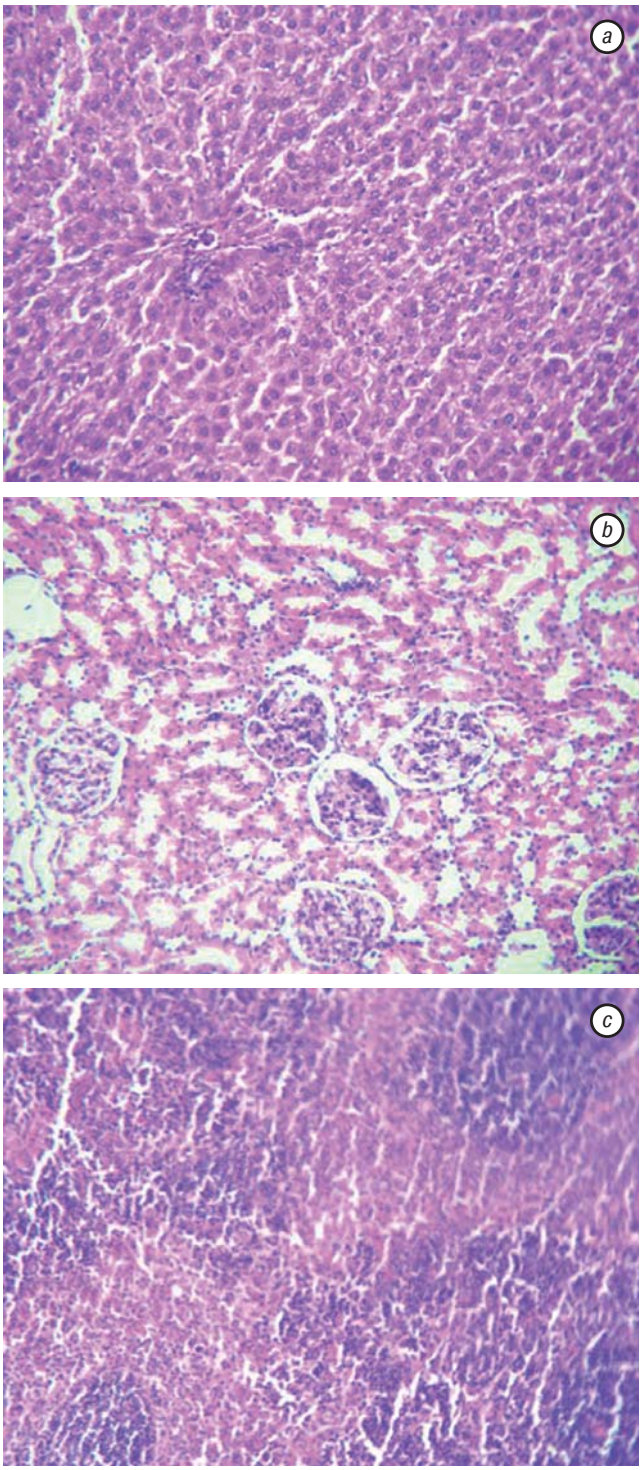

Fig. 2. Morphological structure of innate organs in Guerin carcinoma-bearing rats after ES treatment (x 200): *a* — liver; *b* — kidneys; *c* — spleen

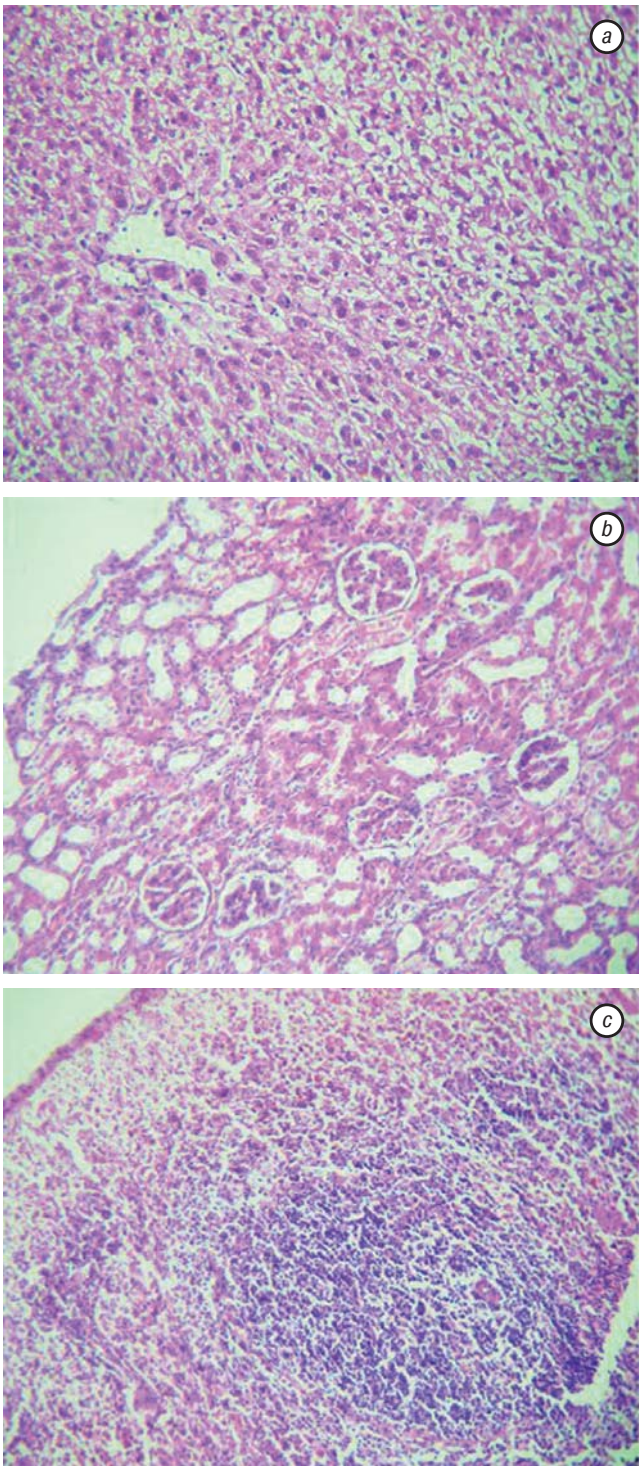

Fig. 3. Morphological structure of innate organs in Guerin carcinoma-bearing rats upon CP treatment: *a* — disruption of liver tissue structure, regions of necrobiosis, appearance of naked nuclei and empty cytoplasm (x200); *b* — dystrophy of functional renal cell elements, tubular necrosis, glomerular destruction and formation of large lumens between the tubules (x200); *c* — devastation of cells in marginal zone of spleen, erythrocyte destruction in red pulpa with appearance of moderate haemorrhages (x100)

significantly lower numbers of erythrocytes, haemorrhages were rare enough. The large majority of cells in tubules are of normal morphological structure, the quantity of lumens between tubules and their sizes were lower. In one animal kidney structure was practically equal to that in healthy rats. Characteristic pattern of spleen was the prevalence of lymphoid follicles with extended marginal zone over red pulpa.

Thus, daily administration of carbon enterosorbents results in significant suppression of systemic toxic reactions of CP. The obtained result could be of great practical importance, however, only in the case if ES doesn't influence anticancer effect of the cytostatic. That's why at the next stage of our research we have analyzed this issue.

An analysis of Guerin carcinoma growth in the groups of rats treated with the enterosorbent or CP alone or in combination has shown that daily administration of enterosorbent caused insignificant tumor growth inhibition and insignificant enhancement of CP inhibiting action (Fig. 5). On day 22 after tumor cell transplanta-

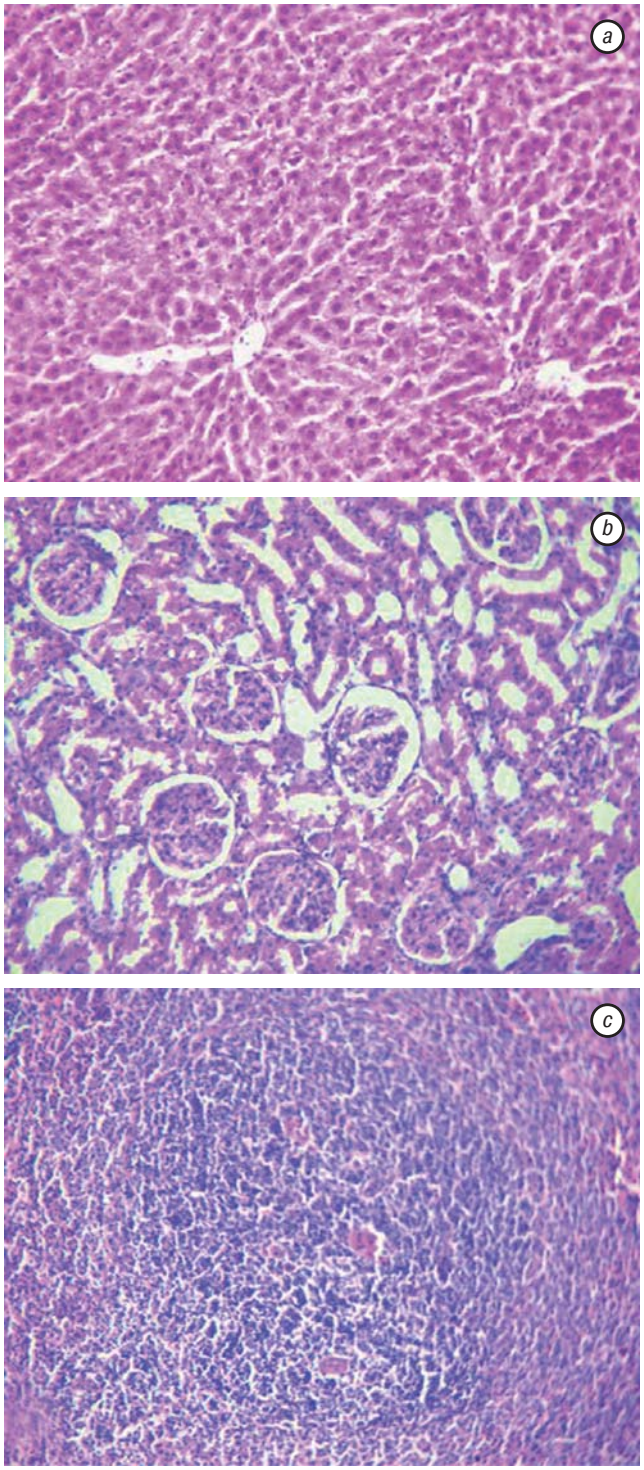

Fig. 4. Morphological structure of innate organs in Guerin carcinoma-bearing rats upon CP+ES treatment (x 200): *a* — appearance of hepatocytes with more basophilic cytoplasm and dense nucleus; *b* — renal tubules possess normal morphological structure; *c* — lymphoid follicle with large marginal zone in spleen

tion an average tumor weight in tumor-bearing rats achieved 37.2 ± 9.5 g, in animals treated with enterosorbent — 27.2 ± 12.6 g, in animals treated with CP and CP + ES — 1.6 ± 2.5 and 1.3 ± 1.6 g respectively. At this day 2 from 7 tumor-bearing rats died, and 1 from 8 animals — in tumor + ES group. Tumor regression was not observed in both groups. In groups treated with CP and CP + ES none of animals died, while tumor absence was observed in 1 and 2 animals respectively.

On day 22 morphological structure of tumor is typical for Guerin carcinoma (Fig. 6 *a*). In some tumors small area of necrosis and the presence of dystro-

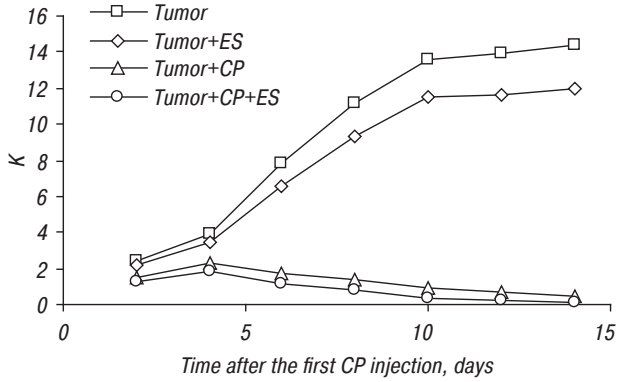

Fig. 5. Dynamic of Guerin carcinoma growth

phy-like altered cells were detected. Administration of enterosorbent did n't significantly alter morphology picture of tumor (Fig. 6 *b*). Upon CP action necrotic regions of different sizes were formed in tumor tissue which were large enough in some animals (Fig. 6 *c*). Connective tissue is observed in moderate quantity as an appearance of separately placed fibroblast-like cells or their accumulations. ES introduction drastically alters morphological structure of tumor. In tumor one could observe large areas of newly generated connective tissue which consists from connective fibers, fibroblasts, macrophages and large number of newly formed blood vessels (Fig. 6 *d*). In connective lining there were detected single tumor cells and single small regions of necrosis. Thus, instead of large necrotic area observed in tumor after CP treatment, the combined action of CP + ES resulted in the death of the majority of tumor cells and in appearance of connective tissue elements. The mechanisms and consequence of such events require the performance of additional studies.

So, the obtained results have shown that potent antitoxic action of enterosorbents which are administrated 1 h after intravenous administration of CP, is realized at the conditions of full preservation of its cytoxic activity. It is known that CP possesses a dose-dependent nephrotoxicity which is characterized by cumulative character and is the main toxic factor which limits its high-dose regimen of use [22]. There is also a significant number of works devoted to altered gene expression in kidney tissue upon platinate action [22, 23]. The conditions of ES performance selected by us had allowed to prevent severe toxic damage of tissues of kidney and other organs caused by toxic action of CP and tumor growth. Among many mechanisms of ES multifactor influence which have been discussed in a number of related studies [24–26], one should consider an evident role of adsorption of toxic products generated in the process of damage of normal and tumor cells as well as intermediate and final toxic metabolites of disturbed metabolism, what prevents their re-sorption and finally decreases metabolic and toxic load on excretion organs, first of all — liver and kidneys. One of the most important properties of enterosorbents, especially carbon ones, is their ability to bind effectively bacterial endotoxins (BET) [27]. In the case of ES introduction into CP chemotherapy, this property of enterosorbents is of particular importance because of the fact that

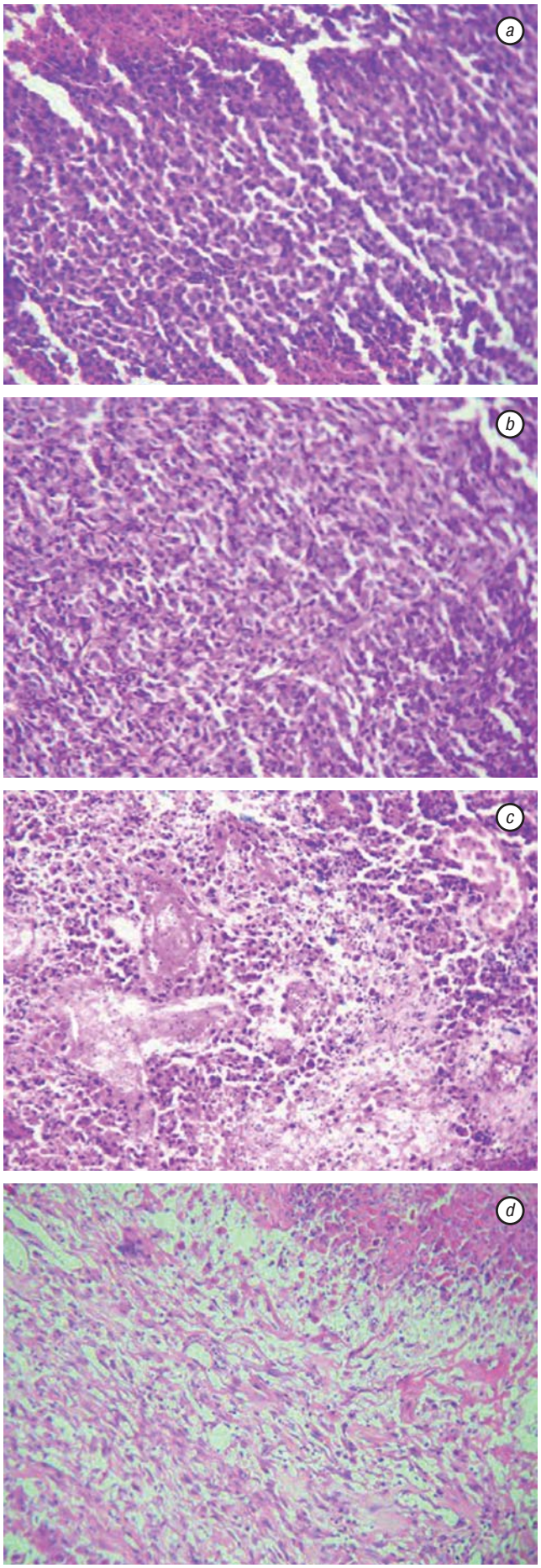

Fig. 6. Morphological structure in Guerin carcinoma on day 22 after transplantation (a); upon ES treatment (b); prevalence of necrotic zones of different sizes upon CP treatment (c); large region of newly generated connective tissue and single necrotic zones upon CP + ES treatment (d).

BET synergistically promote CP nephrotoxicity: single administration of CP or BET to mice doesn't cause renal dysfunction however their combined administration leads to the development of severe renal failure [28].

The obtained results allow conclude that ES at the regimen of daily use of active enterosorbents just 1 h after CP administration possesses detoxicating potential sufficient for significant elimination of toxic effect of the cytostatic at the background of complete preservation of its antitumor activity. Apart from this, a drastic alteration of morphological picture of kidneys in tumor-bearing animals treated by combined CP-sorption therapy compared to that in animals treated with CP alone, allows to suggest that ES could be capable to affect gene expression in kidney tissues; such phenomenon has been registered earlier in the study of effect of carbon eneterosorbent administration on renal failure development modeled in rats [23].

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