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REVIEW

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CARBON ADSORBENTS IN ONCOLOGY: ACHIEVEMENTS AND PERSPECTIVES

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The results of own investigations and literature data are summarized to determine the place of the main methods of adsorption therapy in complex treatment of the patients with malignant tumors. New possibilities for the usage of new generation of carbon adsorbents and modern adsorptive technologies in cancer treatment are discussed.
***Key Words*: adsorptive therapy, hemocarboperfusion, immunosorption, enterosorption, applicative sorption.**

Severe toxicosis observed in cancer patients is manifested by many clinical symptoms including general asthenia, elevated fatigability, adynamia, lability of pulse and pressure, nausea, vomiting, disturbed appetites up to complete anorexia, diarrhea, skin pallor and sallow, xerostomia, xidrosis, fever, myalgia and ostealgia, inclination to peripheral neuropathy, psychic inhibition, cephalalgia and faintness, sleep disorder, anemia, decreased staminas to infectious diseases, dystrophy of muscle tissue and progressive body weight loss with final cancer cachexia. The spectrum of mentioned symptoms in each particular case could vary dependent on the patterns of clinical course of the disease, intensity of destructive processes, treatment type, presence of concurrent diseases and complications, and many other conditions.

Oncological toxicosis is based on several factors. Firstly, it is "tumor disposition", i.e. a special pathological state that develops during the process of natural course of malignant disease and is caused by distant character of tumors' influence on metabolism and host immune status [1–3]. Secondly, tumor-dependent compression or tumor invasion into vital organs and malfunction of excretory-evacuation systems, and also "overloading" of cellular and humoral blood transport agents with waste metabolites lead to expressed disturbance of biochemical homeostasis and metabolic intoxication [4, 5, 6]. The third cause of toxicosis is originated due to the treatment directed on the destruction of neoplastic lesions [7–11]. A certain role is played also by unspecific factors such as surgical trauma, hemorrhagia, inflammatory complications, and sepsis [12, 13].

In accordance with abovementioned, in oncological clinics adsorptive therapy could be applied:

- to remove toxins generated in the process of "natural" tumor-host interaction;
- for correction of metabolic intoxication;
- for sorption of toxins that accumulate due to the destruction/damage of normal and tumor cells with different therapeutic agents, including irradiation;
- for local and systemic control of pharmacokinetics of cytostatic preparations;
- for therapy of surgical complications and concominant toxicosis, for instance, bacterial endotoxicosis of enteric origin that accompanies massive blood loss.

These possibilities are realized by the use of three main methods of sorption therapy, namely: hemosorption (HS), enterosorption (ES) and application sorption (AS).

TYPES AND CHARACTERISTICS OF CARBON ADSORBENTS

Two types of carbon adsorbents — granulated and fibrous ones — are used in adsorptive therapy. Well-known SCN carbons prepared on the basis of synthetic polymeric resins and possessing developed porous structure, specific surface of the order of 1.5 thousands m^2/g and high enough adsorption activity, belong to the first type. New generation of granulated carbon adsorbents with specific surface that reaches 3.5 thousands m^2/g, has been developed in the Department of Physico-Chemical Mechanisms of Sorption Detoxification of IEPOR NASU and was registered in Ukraine and Uzbekistan under HSGD mark (Hemo Sorbents Granulated Deliganding). HSGD, due to effective removal of protein-bound toxic metabolites such as nonconjugated bilirubin, free fatty acids, phenols, bile acids, mercaptanes, and a whole number of uremic and burn toxins during hemosorption procedure, allow to achieve qualitatively new therapeutic effects related to deep purification of transport proteins and blood cell membranes [14, 15]. Clinical use of HSGD columns as a module of "Artificial liver" apparatus or as a separate system for prehepatocytic removal of bile components and their precursors allows remove apiece up to 1 g of bilirubin, with the use of column that contains by 20–30 times lower sorbent

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Abbreviations used: AS – applicative sorption; CP – cisplatin; dHSA – deliganded human serum albumin; EPR effect – enhanced permeability and retention effect; ES – enterosorption; HS – hemosorption; HSA – human serum albumin; HSGD – hemosorbents granulated deliganding; NAB – nanoparticle albumin-bound; SCN – spherical carbonit.

mass than reactors of other modern systems for treatment of hepatic insufficiency.

These super active carbon adsorbents effectively remove also proinflammatory cytokines and could be used for treatment of practically all states associated with the development of Systemic Inflamatory Response Syndrom (SIRS) [16].

Activated fibrous carbon adsorbents for medical purposes that possess high sorption activity too (their specific surface is in a range from 1.5 to 2.5 thousands m^2/g), are used mainly as a basis for preparation of enterosorbents and application sorbents. In the process of production of modern enterosorbents of IV generation — "Carboline", activated carbon fibrous materials are dissected into 40–50 nm fibers which are used for formation of tablets or granules with the use of water as a binding element; this allows to preserve completely preserve the capacity of the sorbent and significantly improve its kinetic parameters.

Both granulated and fibrous adsorbents may serve as a matrix for immobilization of biologically active compounds without using additional cross-linking agents — "binary synthesis". This method has been used for immobilization of native thymus DNA and dextrane sulphate onto granulated and fibrous carbon adsorbents [16]. Coating of superactive carbon matrix with native DNA allows not only to remove DNA-binding compounds that could be present in excessive amounts, for instance in blood of patients with lung cancer or hepatocellular carcinoma, but also significantly intensifies the elimination of proinflammatory cytokines (TNF-α, IL-1, IL-6). An expressed antitumor effect has been registered in 6 from 7 dogs with spontaneous tumors of mammary gland after plasmoimmunosorption on highly active carbon fibers with immobilized devitalized *St. aureus Cowans* I cells [17]. Meanwhile, in 3 animals complete tumor reduction and healing of superficial wounds has been achieved.

CARBON ADSORBENTS IN CANCER TREATMENT

Presently a certain experience of the use of carbon adsorbents in combined therapy of cancer has been accumulated.

Carbon adsorbents in surgery

In surgery adsorptive therapy is directed on preparation of patients with severe intoxication to surgical intervention and elimination of post-surgical purulent-septic complications.

The performance of one or few HS sessions in patients with mechanical jaundice at pre-surgical period allows carrying out extensive surgery without specific complications characteristic for long-term cholemia. After HS in the patients, concentration of bilirubin, bile acids and creatinin decreases, and skin itching vanishes or decreases [18]. HS partially or completely prevents post-surgical fall of fibrinogen level that could be a cause of elevated hemorrhage. The positive effect of HS in patients with mechanical jaundice is in part related to the removal of bacterial endotoxins that pass to systemic blood flow due to malfunction of natural mechanism of their decontamination by conjugation with bile acids. The clinical experience has demonstrated that HS in patients with mechanical jaundice is the most effective if it is performed one day prior to the surgical intervention. In this case the sorbent of choice is HSGD that allows removing large quantities of protein-bound cholemic metabolites.

Modern tactics of treatment of patients with mechanic jaundice of cancer genesis is based on combination of intense infusion therapy with the use of extracorporeal detoxification methods including HS, plasmapheresis, and blood perfusion through xenospleen, that allows reduce early post-surgical mortality by 8.5% [19]. The efficacy of plasmapheresis and HS increases if the procedures are performed after endoscopic detoxification of biliary tract [20].

An alternative means of pre-surgical preparation of cancer patients with liver and kidney malfunction is massive ES (8–24 tablets of "Carboline" enterosorbent per day) that provides quick decrease of intoxication level and improvement of overall health. In patients with mechanical jaundice the use of carbon enterosorbents at pre-surgical period was accompanied by improvement of hepato-renal functions thus allowing to reduce significantly the number of purulent post-surgical complications and lethal outcomes [21].

In principle, prophylactic ES could be indicated in all the cases when surgical intervention is related to the risk of massive blood loss that leads to centralization of blood circulation and effluent of E.coli endotoxin in blood with the next development of SIRS. Then the presence of large amounts of fibrous carbon enterosorbents in large bowel impedes the development of systemic endotoxicosis and uncorrectable hypotension.

HS is an effective element of complex therapy of post-surgical purulent-septic complications. In patients with a generalized peritonitis after surgery related to gastric cancer and cancer of pancreatoduodenal region, HS promotes quick restoration of intestinal peristalsis, decrease of purulent egestas from abdominal cavity and elimination of peritoneal symptoms, improvement of functional state of liver and kidneys, cardio-vascular system and rheologic properties of blood, that results in statistically significant decrease of lethal outcomes [22]. An analysis of efficacy of treatment of patients with a generalized peritonitis has shown that HS should be performed in the first 12–36 hours after laparotomy.

During HS process, in patient blood the level of toxic metabolites including medium molecular weight peptides, decreases, what is caused not only by their effective removal but also by the decrease of total proteolytic activity of blood plasma. A positive consequence of HS is elevation of blood content of mature neutrophils that could be possible caused by de-suppression of active proliferation of stem cells inhibited by toxic factors. The contact of blood cells with the sorbent may cause transitory degranulation

of neutrophils and 100–200-fold increase of lactoferrin level that participates in hemopoiesis regulation, inactivation and elimination of medium molecular weight toxins, in blood plasma. Effluent of myeloperoxidase and lysozyme in blood flow elevates tumoricidal and bactericidal potential of blood. During HS process with the use of deliganding adsorbents, there occurs an intense "purification" of cellular membranes, removal of protein-bound metabolites and correction of transport functions of proteins and erythrocytes.

Detoxification abilities of ES at post-surgical period have been demonstrated with the use of mixed sorbent (polysorb with microcellulose) in the patients with colorectal cancer [23]. Three weeks after surgical intervention, in the ES-treated patients the level of immune complexes was at average by 28% lower that that in control group.

A significant role in post-surgical treatment of cancer patients could be played by AS. Presently there are developed the approaches for the use of applicative adsorbents at different stages of wound process. At early post-surgical period the AC method provides quick sorption of a large quantity (up to 1.5 g per 1 g of the weight of carbon tissue) of different biologically active components from wound, for instance, biogenic amines and mediators of inflammation, as well as toxic products, that leads to attenuation of vascular reaction and intensity of inflammatory events in the wound and surrounding tissues, blocks local sources of intoxication and prevents secondary infection [24]. Finally the terms of wound healing are reduced. For cancer patients an early AS use is especially relevant because surgical intervention performed at the background of intoxication and decreased activity of detoxification systems, often leads to purulent-inflammatory complications.

For treatment of wounds already complicated with purulent infection, sorption-enzymatic complex on the basis of fibrous carbon sorbents with immobilized proteolytic enzymes is of special interest. Immobilization of enzymes could be done also ex tempore from enzyme solution (0.1 g of enzyme per 50 ml of physiologic solution or solution of antiseptics, for instance, chlorhexidine). Such binary system provides effective enzymatic lysis of wound dedritis and denatured proteins and sorption of proteolytic products and tissue toxins. Also, immobilization prevents quick inactivation of enzymes in the wound while decreased viscosity and elevation of osmolarity of wound content upon the action of proteases improves draining properties of carbon material. Carbon fibrous sorbents could serve as a matrix for immobilization of antibiotics including anticancer ones what guarantee the stability of their concentration and the place of contact with wound surface. This allows consider such composites as the means of local chemotherapy. For instance, in a half of cases tumor cells are found in peritoneal lavage of patients with gastric cancer. In such situation intraperitoneal chemotherapy with high local concentration of cytostatics may serve as an effective supplement to surgical treatment.

Carbon adsorbents in chemotherapy

Intense chemotherapy up-to-date remains the most aggressive method of treatment of cancer patients. High systemic toxicity of anticancer means leading to nephro- and cardiopathy, hepatic and gastro-intestinal insufficiency, suppression of hemopoiesis, in a number of cases hinders the performance of chemotherapy courses at the required dose.

During preparation of cancer patients to intense chemotherapy courses and radiation therapy one could use HS or ES methods depending on the endogenous intoxication degree and the presence of complications of tumor process that could be considered as contraindications to HS performance (risk of uncontrolled internal hemorrhage, pulmonary edema, and expressed hypotension). Adsorptive therapy improves patient's state, obviates asthenia, nausea and vomiting, sleeping disorders, eliminates or attenuates tumor anorexia syndrome.

HS at the background of massive chemotherapy accompanied by renal and hepatic insufficiency and cytostatic-dependent myelodepression allows to decrease significantly clinical signs of intoxication, improve function of kidneys and liver, elevate at average by 10% leukocyte blood counts and enables the treatment continuation by radical schemes [25].

In HS process, deliganding sorbents may provide effective removal of protein-bound hepatic and uremic toxins upon cytostatic hepatitis and myocarditis, as well as renal complications of chemotherapy.

Control of pharmacokinetic of cytostatics

HS method affords unique possibilities for control of pharmacokinetics of antineoplastic drugs. Therapeutically valuable differences between concentrations of cytostatics in tumor and the most vulnerable organs are created by regional introduction of massive preparation doses with the following adsorption purification of flowing blood. Just in 70th years of last century there have been proposed two principal schemes of regional chemotherapy that anticipate an effective defense of systemic blood flow with the use of HS [26].

In the first scheme intraarterial chemotherapy is accompanied with adsorption purification of flowing blood under blocking the vessels that unite regional circle with the body. Analogous approach could be used in other variants of local chemotherapy where blood flow "regionalization" could be achieved, for instance with the use of temporary vessel obturation with special catheters. The second variant practically does not differ from well known HS scheme — adsorption circle is connected in definite time after initiation of intraarterial or any other type of local drug administration. Presently an ideology of "adsorption barrier" is successfully developed in experimentally-clinical studies of Japanese scientists who have used HS in the process of intraarterial administration of high doses of cytostatics under venous isolation, and reported on significant improvement of treatment results at the

background of decreased systemic concentrations of the preparations [27–29].

The development of deliganding adsorbents able to provide deep blood purification from free and protein-bound compounds to which belong many anticancer cytostatics, opens the perspective of generation of potent barrier limiting their appearance in systemic blood circulation or minimizing the period of their presence in blood. Sorption system on the basis of deliganding adsorbents, i.e. so-called "quick sorption system", is able to provide durable decrease of systemic concentration of cytostatics and their toxic effects and the apparatus may be connected not only to venous collectors in an area injured by tumor but in any point of systemic blood flow. This is extremely important in such clinical situations when a possibility to perform regional chemotherapy for removal of cytostatics excess from blood is absent in principle. For realization of this approach there is required the sorption system that allows effectively treat nearly 1–2 l of blood per minute, i.e. the one close by its efficiency to apparatus "heart-lungs". All main components required for creation of such system (miniature rotor pumps that do not traumatize blood cells, deliganding adsorbents, systems for control of perfusion parameters and patients' defense) already exist and could be easily united in a single device. Then there'll be created an absolutely new type of cancer chemotherapy where regional intra-arterial administration of high and super-high doses of cytostatics will be associated with practically total absence of toxic effects and safe defense of critical organs.

An important method of adjuvant cancer therapy is ES performed in the process of parenteral chemotherapy.

It has been proven experimentally that ES without decreasing anticancer activity of cytostatics, significantly minimizes systemic toxic action of chemotherapy. In Guerin carcinoma-bearing rats treated by cisplatin at the background daily administration of carbon enterosorbents "Carboline", histologic structure of tissues of kidneys, liver and spleen has been affected at significantly lower degree but the number of tumor cells at apoptotic state was significantly higher than that in tumors of animals treated with chemotherapy in the absence of ES. A useful property of "Carboline" is its ability to bind effectively bacterial endotoxins [30], translocation of which from intestines is drastically elevated in the process of intense chemotherapy.

Massive ES has recommended itself as a safe method of jugulation of symptoms of gastroenteropathy and cytostatic-related myelodepression. Starting from the first days of enterosorbent administration, an intensity of nausea, vomiting, diarrhea, attenuates is diminished and the terms of restoration of leucopoiesis are reduced by 1.5–2 times. In patients with different forms of malignant neoplasia the use of "Carboline" after each course of polychemotherapy, in particular that with platinum drugs, allows to prevent severe toxic consequences related to the III-rd degree of toxicity, and decrease the number of patients whose state is characterized by the II-nd degree of toxicity [31]. Delayed emethogenic toxicity when nausea and vomiting start from the 3rd day after infusion of anticancer drugs, is observed practically in a half of the patients while at the background of ES — not more than in 5%.

In general it's necessary to note that in patients with completely depleted possibilities for cytostatic therapy, combination of HS and ES directed on the prevention of fatal toxic reactions, practically always allows to perform at least one more full-scale course of anticancer treatment.

Carbon adsorbents in radiation therapy

The picture of structural and metabolic alterations observed in cancer patients after extended-field radiotherapy, is similar to that upon acute radiation sickness of medium severity degree. In this regard one could analyze the experimental data obtained during HS performance in dogs that received minimal absolutely lethal radiation dose. Survival of animals in the group treated with intravenous administration of antibiotics and albumin solution yielded just 3.2% *vs.* 68.4 and 62.4% in animals treated with HS for 2 h and 24 h after irradiation respectively [32]. Positive clinical results were obtained when HS has been applied for prophylaxis of post-irradiation reactions in patients with Hodgkin's lymphoma after extended-field and subtotal irradiation. In total, HS performed at early terms after radiation therapy could be considered as an effective method of detoxifying therapy.

ES is not so a quick-acting and effective method of detoxification at post-irradiation period, but it could be used successfully as myeloprotective means. Biweekly ES course has allowed to increase leucocyte blood counts in patients with Hodgkin's lymphoma at average by 2 fold compared with control group. There the percent of patients whose leukocyte numbers were higher than 4×10^9/ml was 3 fold higher and those with leukocyte numbers $2–3 \times 10^9$/ml –2 fold lower after ES course then after conventional detoxifying therapy [33].

Development of the means and methods for prophylaxis and treatment of local post-irradiation complications in cancer patients deserves special attention [34].

The use of carbon fibrous adsorbents with immobilized DNA capable to bind antinuclear factors, at early stage of radiation injuries results in reduced terms of cleaning of radiation ulcer surfaces and appearance of fresh granulations thus providing a chance to intensify radiation therapy. In patients with late radiation injuries in the process of use of these carbon composites, progressive decrease of dermatitis signs and radiation-related fibrosis is observed, thus accelerating the skin plastic performance.

Plastic surgery is among perspective fields for use of AS method. In plastic surgery carbon fibrous adsorbents could be used for preparation of plastic beds and fixation of skin peace, and as well — for acceleration of donor place healing. In patients with

skin melanoma at 2–5th days after finishing of thermoradiotherapy, extended ablation of tumor with the next plastics of wound defect has been performed with splitted perforated skin graft. The use of carbon fibrous adsorbents allowed to decrease by more than 90% the number of cases of skin graft rejection and by more than 30% — the number of complications related to necrotic changes in the graft. The terms of complete healing have been reduced by 1.5–3 folds [35].

So, the methods of adsorption therapy in oncologic clinics could be used for jugulation of intoxication before treatment and in the process of therapy for prevention of complications and for elevation of treatment efficacy, for therapy of post-surgical purulent-inflammatory complications and consequences of chemo- and radiation therapy, and improvement of quality of life of patients with incurable tumor process.

PERSPECTIVE USAGE OF CARBON ADSORBENTS IN CANCER THERAPY

Along with the development of new generation of super active carbon adsorbents and new approaches for their use, the range of tasks that could be solved by sorption therapy expands.

Tumor resistance even to high doses of anticancer drugs remains among central problems of modern chemotherapy. The clinical experience of the last years has shown that just in few days after HC performance, the sensitivity of an organism to steroid hormones, opiate drugs, insulin, desensitizing preparations, and to sulphonamides and antibiotics of penicillin and cephalosporin lines significantly elevates. Taking into account the general patterns, the study of possibility to modify drug resistance in cancer patients using modern methods of sorption seems to be promising enough.

Characteristic patterns of solid tumors, in particular, increased vascular permeability for circulating macromolecules and low level of their lymphatic clearance due to ineffective lymphatic draining, determine predominant accumulation of high molecular weight molecules in tumor tissues — the phenomenon known as Enhanced Permeability and Retention effect — EPR effect [36]. EPR effect is acceptable for macromolecules with molecular weight > 45 kDa, including water-soluble biocompatible polymers and blood plasma proteins [37, 38]. EPR effect created a basis of a passive strategy of targeted delivery of medicinal preparations to tumor tissue. Unique transport functions of human serum albumin (HSA) that is capable to bind reversibly hydrophobic molecules including drugs and to accumulate them in solid tumors allow considering it as a carrier of anticancer cytostatics. There could be selected three main approaches to HSA use in macromolecular systems of targeted drug delivery: coupling of low-molecular weight drugs to exogenous or endogenous albumin, conjugation with bioactive proteins and the technology based on drug binding with HSA nanoparticles (so-called nanoparticle albumin-bound (NAB) technology) [39, 40]. Significant enhancement of anticancer activity of doxorubicin has been achieved its incorporation into the matrix of HSA nanoparticles or by adsorption to the HSA nanoparticles' surfaces [40]. Solvent-based formulations of taxanes, a highly active class of cytotoxic agents, are associated with hypersensitivity reactions. 130 nM nanoparticle of albumin-bound paclitaxel (nab-paclitaxel) was recently used in patients with metastatic breast cancer in whom the combined therapy was unsuccessful. In a randomized phase III study of metastatic breast cancer, nab-paclitaxel was found to have improved efficacy and safety compared with conventional, solvent-based paclitaxel [41]. Among the newest developments one should mention the complexes presented by HSA nanoparticles loaded with doxorubicin and covalently bound to monoclonal antibodies directed against alpha v beta 3 integrins, which expression is up-regulated in various types of cancer. Prepared complexes have shown significantly higher cytotoxic activity in alpha v beta 3-positive melanoma cells than that of the free drug [42]. Doxorubicin-loaded HSA nanoparticles the surface of which is modified by covalent attachment of trastuzumab, have demonstrated a specific trastuzumab-based targeting of HER2 overexpressing breast cancer cells [43].

At present time there have been worked out the optimal technologic conditions for conversion of officinal HSA preparation to its activated form by purification on HSGD hemosorbents [44]. Activated (deliganded) HSA (dHSA) possesses significantly enhanced acceptor capacity of the main discrete binding centers compared with the officinal preparation, and is the perspective transport means in a context of modern macromolecular systems of targeted drug delivery. It has been shown that complex-forming ability of dHSA toward cisplatin (CP) is 1.5–1.7-fold higher than that of officinal HSA preparation [45]. Comparative evaluation of pharmacokinetics of CP and CP in complex with dHSA in Guerin carcinoma-bearing rats has shown that upon intravenous administration of the complex, it differs by prolonged period of presence in blood flow, higher bioavailability, gradual accumulation in tumor and kidneys.

Experimental and clinical data have shown that anticancer activity of widely used cytostatic — cisplatin, is determined not only by its free fraction, but also by the one bound with albumin; so, one could propose a way to elevate antitumor activity of the cytostatic: deep adsorption deligandization of albumin prior to chemotherapy initiation that leads to activation of complex-forming function of the protein that at optimal conditions is capable to bind up to 98% of administered. Such approach is available also for protein-bound anticancer cytostatics, including doxorubicin, adryamycin, metotrexate, etc.

Another perspective field of cancer therapy is based of modulating intervention into metabolic relations between tumor and host by removal of essential aminoacids, for instance, L-tryptophane, 80% of which

is bound with blood serum albumin. Dr R. Bambauer (Germany) has decreased L-tryptophane content in blood of cancer patients by 50–60% using multiple HS sessions, and has achieved clinically significant regression in 21% of the patients, and in 14% of the patients — complete elimination of primary tumor lesion and metastases [46]. It's necessary to note that all the patients have been ascribed by ethic commission as completely futureless for further surgical treatment, chemo- and radiotherapy. Let's note also that HSGD sorbents are at least ten times more effective for L-tryptophane removal than activated carbons of Gambro company (Sweden), that have been used by Dr. R. Bambauer in his studies [47].

Thus, the newest carbon adsorbents occupy a notable place in combined therapy of cancer patients and possess undoubted potential for further expansion of their application in cancer treatment.

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