

THEORETICAL GROUND FOR ADSORPTIVE THERAPY OF ANTHRACYCLINES CARDIOTOXICITY

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Anthracyclines play an important role in treatment of variety types of cancer due to their high effectiveness and broad spectrum of activity. However, a major limitation of their use is the dose-limiting cardiotoxicity. The inability to predict and prevent anthracycline cardiotoxicity is in part due to the fact that the molecular and cellular mechanisms remain controversial and incompletely understood. This review focuses on the biochemical basis of the anthracyclines toxic cardiac effects and pharmacological measures to their treatment and preventing. We describe the theoretical substantiation of the enterosorption abilities for diminishing of cardiac damage.

Key Words: anthracyclines, cardiotoxicity, enterosorption.

Anthracyclines (doxorubicin, daunorubicin, epirubicin and others), taking into account their high effectiveness in the treatment of significant number of tumors, nowadays remain the most in-demand class of chemopreparations used in oncological practice, including pediatric oncology [3, 24, 118, 130].

By chemical structure these preparations are represented by hydrotetracenequinone chromophores containing three planar hexatomic rings which are linked with one or several sugar residues. The differences between separate preparations are related to the structure of aglycone or hydrocarbon part of the molecule (Fig. 1) [111].

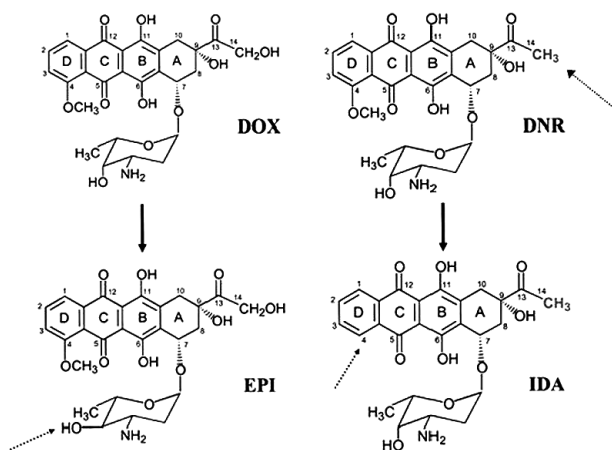


Fig. 1. Chemical structures of main anthracyclines: doxorubicin (adriamycin) — DOX, daunorubicin — DNR, epirubicin — EPI, idarubicin — IDA. The differences between drugs are marked by arrow

The mechanisms of therapeutic action of anthracyclines are very multivarious [27, 67]: 1) DNA intercalation and suppression of macromolecules synthesis;

2) generation of free radicals with the following activation of lipid peroxidation (LPO); 3) binding with DNA molecule and its alkylation; 4) direct action toward membranes; 5) initiation of DNA damage by inhibition of topoisomerase II; 6) induction of apoptosis.

Anthracyclines possess expressed radiomimetic properties: the dynamics of disorders of blood system has a lot in common with the picture observed upon ionizing radiation injury [6, 26]. As well as other intercalating agents, anthracyclines are capable to suppress an activity of DNA repair enzymes. It is known that the synthetic phase of cell mitosis and the transition point of presynthetic phase into synthetic one are the most sensitive to polychemotherapy. Anthracycline antibiotics implement their cytotoxic action simultaneously at different phases of mitotic cycle what determines their high therapeutic activity and in parallel — significant side effects.

One of the most available and effective preparations of this group, doxorubicin (DOX, adriamycin) is a derivative of rubomycin — 14-hydroxyrubomycin, and it is an irreplaceable component of Breast cancer treatment protocols, adjuvant and neoadjuvant chemotherapy of solid tumors in children, soft tissue sarcomas, aggressive lymphomas and hemoblastoses [67]. In the organism DOX is transformed into 13-dihydrodoxorubicinol (DOXol) by dint of cytochrome P450 system and finally — into free radical state of semiquinone type. Free radicals of this anticancer antibiotic quickly react with molecular oxygen and promote an accumulation of LPO products and damage of structural and functional organization of cells' systems [27].

The main side effects of anthracyclines are typical for the majority of antineoplastic preparations and are represented by nausea and vomiting, bone marrow depression, damaging of intestinal epithelium of and other mucosal surfaces as well as hair follicles, suppression of reproductive function, etc. [125]. Differential peculiarity of DOX, as well as other anthracyclines,

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Abbreviations used: cTnT — cardiac troponine T; DOX — doxorubicin; DOXol — doxorubicinol; DNR — daunorubicin; EPI — epirubicin; HF — heart failure; IDA — idarubicin; DCMP — dilated cardiomyopathy; CHF — congestive heart failure; LMW Fe(II) — low molecular weight Fe(II); LPS — lipopolysaccharide; NT-proBNP — N-terminal prohormone of brain natriuretic peptide.

is its significant cardiotoxic action along with other side effects characteristic for the majority of cytostatic agents. Dose dependent injury of cardiac muscle is considered the most significant factor that limits the use of the preparations related to this type [34, 37].

Acute and especially chronic DOX cardiotoxicity leads finally to fatal dilated cardiomyopathy (DCMP), and results in so dangerous clinical manifestations (in the case of development of congestive heart failure (CHF) the mortality rate reaches 60% [132]), that modern schemes of monitoring of side effects of anthracycline chemotherapy prescribe an evaluation of left ventricular ejection fraction before treatment initiation and after achievement of 1/2 of cumulative dose with the following measuring of this index after each new treatment course with the use of anthracyclines and continuation of such control on 3rd, 6th and 12th months after therapy termination [21]. According to other data, 50% of patients which had experience of anthracycline chemotherapy die from CHF caused by their cardiotoxicity during two years from the moment of diagnosis of anthracycline cardiomyopathy despite the performed therapy [41, 113].

There are the following risk factors of cardiac lesion development: 1) cumulative dose of the preparation > 550 mg/m² and higher (after an achievement of cumulative dose, as a rule DCMP develops during a year); 2) age (under 3 and after 65 years); 3) radiotherapy of mediastinum; 4) simultaneous administration of other cardiotoxic agents; 5) female gender; 6) concomitant cardiac pathology; 7) bolus administration of the preparation [35]. The cases of CHF development have been reported also for obtained cumulative dose that was twice lower than the critical one [62, 114].

The mechanisms of damage of the heart upon anthracycline cardiomyopathy are multiple and are not completely studied yet. It is supposed that cardiotoxicity is related to generation of free radicals by “anthracycline-iron” complex and injury of myocardium caused by LPO products [45, 67]. EPR-studies have shown that during this process mitochondrial, nuclear and microsomal reductases catalyze an attachment of electron to quinone residue of tetracycline ring of anthracyclines leading to formation of semiquinone free radical that generates superoxide anion radical O₂^{•-} and hydrogen peroxide H₂O₂. Toxicity of the latest multiply increases upon reaction with low molecular weight iron (LMW Fe). In this case, ferritin is a physiologic protector that serves as a safe storage of cytosol source of high molecular weight iron compounds in soluble and nontoxic form. However, LMW Fe could be replaced from this transport form by O₂^{•-} radical and anthracycline semiquinone radicals [131]. In the majority of cells defense enzymes of antioxidant system (superoxide dismutase, catalase and glutathione peroxidase) reduce to minimum the damaging action of these factors, but the pool of endogenous antioxidants of cardiomyocytes is very limited and couldn't provide adequate reaction

to anthracycline-induced oxidative stress what finally leads to degeneration and descent of cardiac muscle contractility (Fig. 2).

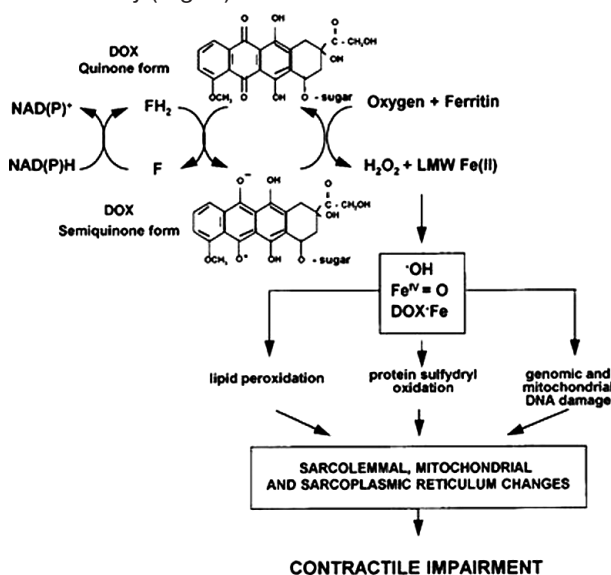


Fig. 2. The “iron and free radical hypothesis of cardiotoxicity of anthracyclines (DOX)”. F/FH₂ — oxidized/reduced flavoproteins (e.g., NADH dehydrogenase, NADPH cytochrome P450 reductase); LMW Fe(II), low molecular weight Fe(II); •OH, hydroxyl radical; Fe^{IV}=O, ferryl ion; DOX•Fe, doxorubicin-iron complex

By an opinion of some authors, as an alternative to a theory of free radical injury of cardiomyocytes, or as its supplement, so called “metabolic” theory could be considered [37, 62, 67]. DOX cardiotoxicity could be explained by cardiac muscle accumulation of its highly reactive alcoholic metabolite doxorubicinol (DOXol) that inhibits Ca²⁺, Mg²⁺-dependent ATPase of sarcoplasmic reticulum, f₀-f₁ proton pump of mitochondria and transport of Na⁺-Ca²⁺ in sarcolemma, thus disturbing intracellular energetic metabolism, ion gradients and balance of Ca²⁺ [62, 66]. It is known that mitochondria, the main suppliers of ATP to cells, yield up to 30% of total myocardium weight. An important factor that promotes toxic action of DOX on cardiomyocytes, is its high affinity to cardiolipin — anionic phospholipid which is specific for mitochondrial membrane and important component supporting of mitochondrial structure and function as well as total energetic metabolism and survival of cells [28, 42, 73]. Another factor of cardiotoxicity caused by DOX is the violation of mitochondrial membrane permeability [70].

In a number of studies there has been found a tight relation and certain prognostic value of elevated level of proinflammatory cytokines, especially tumor necrosis factor-α (TNF-α), Interleukin-1β (IL-1β), Interleukin-6 (IL-6), and their soluble receptors with the intensity of heart failure (HF) and decreasing of left ventricular ejection fraction. Elevated cytokines' level in case of HF is not only a marker of immune activation, i.e. epiphenomenon of severe course of disease, but also it directly affects the development of myocardial dysfunction and remodeling of left ventricle [65, 126]. The mostly studied effects of TNF-α are negative inotropic action, myocardial remodeling, and myocardial

fibrosis, reinduction of fetal phenotype of myocardium, apoptosis of cardiomyocytes, endothelial dysfunction, skeletal muscle myopathy, myocardium cachexia [56]. Increased levels of Interleukin-8 promote the development of insulin resistance and diabetes mellitus in patients with DCMP [8].

In last time there is actively discussed the theory of cardiomyopathy development as a consequence of endotoxemia (Fig. 3). Colon that serves as the main depot of bacterial endotoxins (LPS) is sensitive to damaging action of antitumor preparations. Injury of colon mucosa, edema and ischemia of enteric wall promote bacterial translocation leading to release of LPS, immuno-inflammatory activation and cytokines release [47, 107].

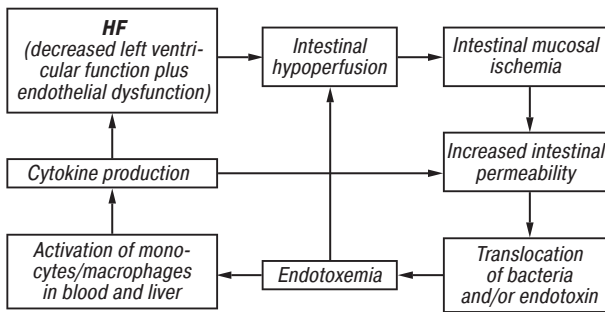


Fig. 3. The role of the gut in HF [Krack A et al., 2005]

It's important to note that approximately 30% of DOX is eliminated with bile in unaltered form thus causing additional cytotoxic action toward intestinal mucosa [2].

As other genotoxic drugs, DOX initiates p53-mediated cell death [117]. It is known that p53 gene is an important regulator of cell division and death. It has been demonstrated that its chemical inhibition prevents DOX-induced cell death and the loss of mitochondrial membrane potential [52]. There have been described also alterations of vasoactive mediator production upon HF development, in particular, of endothelin-1 and nitric oxide [15, 23, 104]. Vasoconstrictive cytokines, endothelin-1 and big endothelin-1, which are responsible for contractility, arrhythmogenesis and remodeling of myocardium, are related also to the category of prognostic indicators of patient's survival ill with HF [43, 61, 95] and play an important role in pathogenesis and progression of cardiomyopathy.

Certain role in CHF development is thought to be related to oxidant-dependent activation of heat shock factors by DOX with the following expression of heat shock proteins (Hsp): Hsp25 which leads to actin destruction [123], and Hsp60, which functions mainly in mitochondria [44]. Also, there have been described such processes as enzymatic activation of binding of DOX with nuclear DNA [112], selective alteration of cardiac mRNA coding important protein of myocardium as α -actin [91], and elevation of phospholipase activity mediated by LPO [83]. Some investigators attach great importance to dysfunction of calcium channels [116], proteolysis of titin (known also as connectin which plays an important role in muscle contractility), and disintegration of cardiac transcription factors concordance [19, 33].

Subclinical myocardial damage caused by anthracyclines could be diagnosed with the use of standard ECG, Holter monitoring, high resolution ECG, evaluation of heart rhythm variability, echocardiography, radionuclide ventriculography, myocardium scintigraphy, magnetic resonance tomography, analysis of concentrations of cardiac enzymes and other biochemical markers of cardiomyocyte damage [128]. However, upon subclinical heart damage, the majority of routine monitoring methods demonstrates low prognostic sensitivity while myocardial biopsy is an invasive process, technically complex and unsafe [4, 89]. That's why the use of biochemical markers for monitoring of anthracycline based chemotherapy and selection of prophylaxis of cardiomyopathy development in patients without notable manifestations of myocardial damage seems to be more reasonable. Presently, the use of lactate dehydrogenase (LDG) and creatinphosphokinase (CPK) is not recommended because of their low specificity. In this sense, natriuretic peptides (atrial natriuretic peptide — ANP and brain natriuretic peptide — BNP) are more informative. These neurohormones play a key role in the support of compensated state in patients with initial CHF manifestations, firstly, due to their influence on renal homeostasis, water-electrolytic balance and renin-angiotensin-aldosterone system at the conditions of decreased cardiac ejection. Terminal fragment of BNP precursor — NT-proBNP (**N-terminal prohormone of brain natriuretic peptide**) — has more prolonged half-life period, so the latest studies have been done with NT-proBNP which is secreted in heart ventricles in response to volume and pressure overloads [21]. Blood plasma content of NT-proBNP and BNP are increased during the first year after chemotherapy with moderate anthracycline doses [16]. It is necessary to note that there have been obtained no valuable proofs of prognostic significance of natriuretic peptide levels, but an increase of their blood plasma concentration could be used for selection of patients with higher risk of heart dysfunction development in late-term and respectively these who require more intense supportive therapy. There has been also detected a relation between concentration of carnitine, lipid peroxidase level in blood plasma and myocardial dysfunction [11, 50].

Despite a large number of proposed biochemical markers, the most reliable method of myocardial dysfunction prognosis is considered to be determination of level of cardiac troponin T (cTnT) which is excreted in blood due to cardiomyocyte membrane destruction [82]. **In many studies it has been shown that even moderate elevation of cTnT induced by DOX, is associated with histological signs of myocardial damage** [36].

By clinical patterns one could distinguish acute and chronic cardiotoxicity [37, 50, 129]. Acute form develops at the moment of administration of the preparation or few hours after it and is manifested by transitory arrhythmia and hypotension that could be treated effectively. Chronic cardiotoxicity leads to the development of congestive HF that is refractory to standard inotropic

agents [66]. Some authors distinguish its early form (which occurs during the first year) and late form (that develops from 1st till 30th years with the pike at 7–10th years) [62]. Creutzig U. et al. [17] point out that more often chronic cardiomyotoxicity develops in children who already underwent an acute form of cardiomyotoxicity or received repeated treatment courses with anthracyclines, even in the cases when the preparations with lower cardiotoxic potential have been used.

Taking into account the facts that in people with survival **higher than 5 years after anticancer treatment** with the use of anthracyclines, the mortality risk related to heart pathology is 10 fold higher than that in total population [99], **as well as nearly 60% of patients** who survived after childhood cancer, receive the preparations exactly from this group [102], the search for effective methods of prophylaxis and mitigation of cardiotoxic effects of anthracyclines is extremely actual. First of all, it is the screening for risk factor presence in the patients, correction of cumulative dose of anthracyclines, and active monitoring of subclinical myocardial damage [4]. The synthesis and development of new preparations with lower cardiotoxic action including their liposomal forms, is important, too [13, 38, 97, 105, 119]. Also, it is reasonable to use active curative-prophylactic administration of cardioprotectors with antioxidant properties, in particular, organic amifostine thiosulphate [94], L-carnitine [133], N-acetylcysteine, vitamin E [40], thiotriazoline [14], flavonoid rutoside [121], etc. There are also used cholesterol-depletion agent probucol [49, 58], beta-blockers [63], calcium channel inhibitors [69, 122] and their combination with activators of ATP-sensitive potassium channels [68]. Rovustatin and probucol possess fine antiapoptotic potential toward cardiomyocytes and are classic lipid-lowering drugs [84, 106]. There is also known a cardioprotective effect of adenosine that increases intracellular ATP concentration and adenylate potential in total [72]. By the data of Cardinale D. et al., early administration of ACE-blocker enalapril nearly totally prevents the development of HF in the risk group [12]. However, in **analogous study devoted to cardioprotective action** of enalapril in children who underwent intense chemotherapy, the use of this preparation resulted just in moderate effect [110]. Interesting experimental results have been recorded upon the use of erythropoietin, thromboplastin, and synthetic prostacyclin iloprost usually used for treatment of pulmonary arterial hypertension, as cardioprotectors [53, 55, 71]. By our opinion, **the use of granulocyte colony stimulating factor** for prophylaxis of DOX-induced DCMP seems to be especially perspective [54], because this cytokine is simultaneously the most potent myeloprotective agent. Iron-chelating agent cardioxane demonstrates good results in prophylaxis of acute and chronic DOX-induced cardiomyopathy; however, its influence on efficacy of cytostatic anthracycline-based therapy is speculative [29, 32, 57]. Cardioxane usage

is limited by its characteristic myelotoxicity, nausea and diarrhea [25].

So, despite intense scientific efforts, the mechanisms of cardiotoxicity development upon anthracycline-based chemotherapy remain incompletely studied yet while the possibilities of modern preventive and curative strategies, unfortunately, are still limited. An absence of safe methods of prophylaxis and treatment of anthracycline cardiomyopathy forces the search of new ways to solve this problem. From this point of view, the use of modern approaches of sorption therapy is very perspective. **It is known that sorption technologies** are among the main components of **effluent medicine — science about curative measures** directed toward removal of toxic compounds of endogenous and exogenous origin from body fluids [74]. The most widely used types of sorption detoxification are purification of blood and its components by hemosorption, oral administration of large doses of sorption materials, and also application sorption therapy of burns and wounds. It is commonly known that in cancer patients an expressed endogenous intoxication is determined by tumorigenous process as well as by curative means **directed toward destruction** of malignant lesions [76]. So called “**tumor disposition**” (the state developed during natural course of malignant pathology) is based on the stable LPO activation, development of oxidative stress [59], and “**metabolic intoxication**” which is related to dysfunction of excretory organs, i.e. accumulation of excessive amounts of toxic intermediate and terminal **metabolites** [100]. **Thus, the necessity of use of detoxification means and methods in oncology is evident.** For example, upon DMCP there have been received positive results of plasmaimmunosorption that were expressed in decreased level of a NT-pro BNP marker and significant elevation of ejection fraction from 25.5 to 30.9% [20]. Very perspective and effective in such cases could be **another method of detoxification — enterosorption** that is noninvasive in contrary to hemosorption, and plasmapheresis.

The term “enterosorption” has been used since 1982 [77].

Local mechanisms of curative action of enterosorbents [Nikolaev V.G., 2009]:

- 1) adsorption of exogenous toxic compounds;
- 2) adsorption of toxins that diffuse in intestinal lumen from blood;
- 3) binding of toxic compounds excreted together with digestive juices;
- 4) adsorption of toxic metabolites generated in GIT (indol, skatol etc.);
- 5) sorption modification of diet via selective adsorption of its compounds;
- 6) fixation and transfer of physiologically active compounds (enzymes, bile acids etc);
- 7) enhancement of indigestible residue volume by the type of action of dietary fibers;
- 8) catalytic action;
- 9) coating and cytoprotective action;
- 10) structuring of intestinal content;
- 11) formation of aggregates and flocculates containing microbes and viruses;
- 12) direct bactericidal action;
- 13) complex formation and chelating
- 14) modification of chemical composition of intestinal content hindering pathogenic flora propagation;
- 15) normalization of enteric microbiocenosis;

16) elimination of meteorism, improvement of blood supply of intestine, stimulation of peristalsis.

Systemic (extraintestinal) effects of enterosorption are: 1) **prevention or attenuation of toxico-allergic reactions**; 2) **prophylaxis of somatogenic stage of exotoxicosis**; 3) decreasing of metabolic load on excretory and detoxification organs; 4) positive correction of a number of metabolic processes and elements of immune status; 5) improving of humoral homeostasis, elimination of imbalance of biologically active compounds; 6) **restoration of integrity and penetrability of cell membranes as well as regenerative potential of organs and tissues**; 7) suppression of LPO processes; 8) improvement of lipidogram indexes; 9) normalization of cytokine profile of blood plasma [5, 78].

Multifaceted action of enteral sorption detoxification has made it an important component for treatment of such pathologies as acute intestinal infections [81], colitis and enterocolitis, dysbacteriosis [108], various intoxications [90], kidney diseases [22], especially which are accompanied by chronic renal insufficiency [75], and also atherosclerosis, diabetes mellitus, bronchial asthma, viral hepatitis, some autoimmune and skin diseases [109].

Influence of enterosorption on the development of oxidative stress has exceptional importance. It is known that increasing of usual speed of free radical oxidation serves as universal mechanism of development of many pathologic processes [51]. In experimental studies there has been shown an efficacy of silicon-organic enterosorbent Enterogel for decreasing the content of LPO products and improvement of antioxidant defense at the background of usage of combined antituberculosis drugs [86, 93]. **Also there has been described an effectiveness of chitosan for correction of excessive LPO upon the use of rifampicin and isoniazid [103].** Introduction of Polysorb into treatment schemes for patients with tuberculosis increases an efficacy of polychemotherapy and decreases the manifestation of **side effects [39]. Administration of SUMS-1 enterosorbent decreases the LPO level, affects the shape of pharmacokinetic curves for isoniazid without alteration of total area under the curve, and attenuates drug resistance to some groups of antibiotics [46].** It was found the decreasing of negative influence of excessive LPO by enterosorbents improves prognosis upon toxic and viral hepatitis [98, 124]. There has been registered a **positive effect of enterosorption in case of congestive HF developing due to ischemic heart disease and arterial hypertension.** Schemes which included carbon sorbent SCN and cardiac glycosides were by 21% ($P < 0.05$) more effective than the use of strophanthin or digoxin without SCN [80]. Enterogel successfully **protects the membranes and stabilizes hepatocyte lysosomes during aggressive anticancer chemotherapy [30].** In mentioned study cyclophosphamide, vincristin, and prednisolone were administered to rats. In groups with concomitant Enterogel usage (1 g/kg for 7 days after **cytostatics administration**), **there has been observed the decreasing of cytolysis markers (ALT, AST**

and lysosomal enzymes. So, as it has been mentioned above, enterosorbents reveal expressed distant effects without systemic pharmacokinetics and significantly decrease toxic loads on excretory body systems [90, 127], as well as endogenous intoxication level upon severe infectious diseases [1] and burns [87, 120].

Cytokines are universal regulators of homeostasis, which may initiate multiple pathologic processes [60]. The **decreasing of the level of proinflammatory cytokines** upon the influence of enterosorbents observed in the case of thermal trauma [88], food allergy [64, 85], **intestinal infection and measles [115], pancreonecrosis [96], creates abilities for effective use of enterosorbents** in a number of other clinical situations including anticancer chemotherapy.

There have been described positive clinical effects of carbon sorbent SUMS-1 in cancer treatment what allowed to **decrease the dosages of analgesics, myelotoxicity of polychemotherapy, and level of endogenous intoxication [10].** Granulated carbon enterosorbent SCN have demonstrated the decreasing of rubomycin myelotoxicity in rats with inoculated tumors as well as the presence of moderate leukostimulative effect upon clinical polychemotherapy [9]. Also it has been shown that carbon enterosorbent Carboline possess notable **antiemetic activity upon different polychemotherapy schemes [92].** In patients with resectable colon cancer **an introduction of enterosorption into the complex of curative actions** has decreased the frequency of side effects development from 7.4 to 2.9%, and increased total 5-years survival from 66.1 to 79.3% [18].

Adsorption of endogenous toxins generated in intestines has a special value in the cases when barrier function of intestinal epithelium is attenuated, in particular upon cytostatic therapy. In such situation the presence of potent adsorbents in intestinal lumen prevents translocation of increased amounts of natural products of enteric metabolism (indols, phenols, scatol etc.), bacterial toxins, and intestinal microflora into bloodstream [5, 74]. Beneficial effects of enterosorption in acute intestinal infections is determined by a complex of factors: adsorption of bacterial toxins and inflammatory mediators, elimination of secretory diarrhea, total change of chemical composition of enteric content, suppression of pathogenic microflora growth [74, 81]. Also Enterogel is capable to adsorb enteric bacteria on its surface and destruct some of them [79]. Enterosorbents decrease adhesion of microorganisms of the surface of intestinal mucosa and bacterial translocation [48]. Enterosorbent-bound microorganisms, toxins and metabolic products are removed from a body and therefore, enterosorption decreases LPS level [31, 101]. **Prolonged administration of SUMS-1 enterosorbent promoted an increase in the number and height of microvillus in small bowel, activation of mitochondrial apparatus of enterocytes, and possibly total elevation of their adaptive potential [7].** So, enterosorption which is widely used in treatment of pathologies of gastrointestinal tract and affects their various pathogenic moments, seems to be very perspective for treatment

of gastroenteropathy which develops due to cytostatics application, and also for binding of anthracyclines excreted with the bile, **because enterohepatic recirculation** of the latest enhances their cytotoxic effect toward intestines and liver.

Taking into account the abovementioned role of **LPO activation, proinflammatory cytokines, bacterial endotoxins in the development of cardiotoxic effects** of anthracyclines, and in particular, DOX, as well as positive effects of enterosorbents in oncological clinics and experimental oncology, one could consider reasonable to include enterosorption into the schemes of **anticancer therapy with the use anthracycline antibiotics** for decrease of their system toxicity, first of all, cardiotoxicity.

Hemocarbo-perfusion which exhibits evident parallels between mechanisms of its action and mechanisms of development of anthracycline cardiotoxicity, also looks to be prospective method of the treatment of immediate and late cardiac complications of anthracycline chemotherapy.

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