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Chapter

Sorption Detoxification as an Addition to Conventional Therapy of Acute Radiation Sickness and Iatrogenic Leukopenia

Oksana O. Shevchuk, Elisaveta A. Snezhkova, Anatoliy G. Bilous, Veronika V. Sarnatskaya, Kvitoslava I. Badakhivska, Larysa A. Sakhno, Vasyl F. Chekhun and Volodymyr G. Nikolaev

Abstract

Leukopenia is an essential part of the clinical course of acute radiation sickness and is a side effect of anti-cancer treatment. In both situations, the main factors which determine the survival are the degree of bone marrow suppression and gastrointestinal tract damage due to the presence of a large pool of fast-dividing cells. Leuko- and neutropenia are main limiting factors which may contribute to chemotherapy failure. Hematopoietic cytokines the part of conventional therapy in this field, but their effects require boosting. That is why the use of means and methods of adsorption therapy is considered promising. Sorption therapy creates a basis for sorption detoxification, a doctrine of curative measures directed to the removal of toxic endogenous or exogenous compounds from body fluids. The most widely used types are the purification of blood or its components (hemosorption), oral administration of sorption materials (enterosorption) and application-sorption therapy of wounds and burns. In this chapter, the results of early and recent research and prospects for the use of carbon adsorption therapy for the treatment of acute radiation sickness and cytostatic myelosuppression are discussed.

Keywords: leukopenia, ionizing irradiation, anti-cancer chemotherapy, granulocyte colony stimulating factor, hemosorption, enterosorption, application-sorption therapy

1. Introduction

The danger of acute and chronic radiation injuries, which provoke leukopenia, is not just a myth today. The explosion at Unit 4 of Chernobyl Nuclear Power Plant (NPP) in 1986 showed how unprepared people were to such a problem. The collective dose of irradiation for liquidators (clean-up workers) was huge; no one knows the exact numbers (all dosimetric equipment measured only gamma irradiation). And until today, about five million people, who live in areas of Belarus, the Russian

Federation and Ukraine, which are contaminated with radionuclides, still experience the consequences of pollution [1–3]. An earthquake and tsunami struck Fukushima Dai-ichi NPP in 2011 contaminated the soil and water with radioactive cesium, iodine, etc. It poses significant risks of exposure to the residents [4, 5]. Terroristic threats or military conflicts with the use of radioactive weapons could be considered as a potential risk of injuries also.

One more source of contact with myelosuppressive factors is radiation therapy, which is routinely used in oncology (up to 70% of patients with malignant tumors are treated with) as well as anti-cancer chemotherapy with cytostatics [6–8]. Medical use of radiation accounts for 98% of the population dose contribution from all artificial sources and represents approximately 20% of the total exposure. Annually worldwide, more than 3600 million diagnostic radiology examinations are performed, 37 million nuclear medicine procedures are carried out and 7.5 million radiotherapy treatments are given [9]. In spite of side effects, the concomitant use of radiotherapy and chemotherapy resulted in significantly improved clinical outcomes [10–12]. Different radiomimetics have effects similar to ionizing irradiation. Among them, a lot of anti-cancer drugs and leukopenia is a common side effect of dose-dense and dose-intense tumoricidal chemotherapy.

The organs and tissues with high speed cell proliferation is the most sensitive for radiation- and radiomimetic damage. Leukopenia, because of aggressive direct ionizing irradiation or anti-cancer chemotherapy with cytostatics, is an important prognostic factor for overall survival [13, 14]. The association between chemotherapy-induced leukopenia and clinical outcome has been reported for several types of cancer. The development of such health impairments gains more and more attention, especially after the success of modern techniques such as stem cell transplantation and cytokine treatment to restore hematopoietic functions. But even now, it is not enough for the treatment of acute radiation sickness.

In last decades, we observe combined injury by ionizing radiation and toxic effects of xenobiotic, thermal burns, mechanical trauma, etc. Despite significant achievements in oncology, precise and targeted irradiation of tumors, the development of effective means for enhancement of bone marrow cell and peripheral blood cells proliferation (granulocyte colony stimulating factors (G-CSF), erythropoietin, interleukin-11 and others), the problems of fighting the negative consequences of ionizing radiation and radiomimetics remain very important.

In this chapter, the results of early and recent research and prospects for the use of carbon adsorption therapy for the treatment of myelosuppression caused by acute radiation sickness and cytostatics use are discussed.

2. About radiation injuries

Acute radiation syndrome is a definition to reflect severe damage to specific organs that occurs because of whole-body or significant partial-body irradiation greater than 1 Gy, over a short time period (high dose rate) [15]. The main syndromes are hematopoietic (doses >2–3 Gy), gastrointestinal (doses 5–12 Gy) and cerebrovascular one (doses 10–20 Gy) [16]. Depending on exposed and absorbed doses and its duration, cells exposed to ionizing radiation or radiomimetics present DNA mutations, apoptosis, necrosis, chromosomal aberrations or increased mutation frequency [17, 18]. The most profound injury is to lymphoid organs (lymphatic nodes, spleen and thyroid gland), bone marrow, testicles, ovaries, gastrointestinal mucosa. Parenchymal organs, namely liver, adrenal glands, kidneys, salivary glands and lungs possess quite high radioresistance. According to World Health Organization (WHO), acute radiation sickness (ARS) is composed of the hematopoietic subsyndrome

(HS), gastrointestinal subsyndrome (GIS), neurovascular subsyndrome (NVS) and cutaneous subsyndrome (CS) [19]. The main factors which determine the survival of victims are the degree of bone marrow suppression and gastrointestinal tract damage due to the presence of a large pool of fast-dividing cells [20–22]. Acute radiation sickness (ARS) could be considered as a sequence of immediate radiation injury and long-lasting bystander cross-effects.

Management of patients with ARS includes early use of hematopoietic cytokines, antimicrobials and transfusion support; in addition, antiemetic agents and analgesics, and even hematopoietic stem cells transplantation [16, 23]. Since 1997, granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) are used and their doses are driven by the radiation dose and physiologic responses for ARS [24] and by clinical protocols for leukopenia and neutropenia caused by anti-cancer treatment [25, 26]. However, these drugs still are of high cost, and pharmacoeconomic benefits seem to be questionable [27]. Singh et al. concluded that cytokine therapy has significant but modest effects [28]. All these facts force the researches to search new methods and means for additions to the management of post-aggressive iatrogenic leukopenia and related ARS- and radiomimetic-induced damage.

3. Adsorptive hemoperfusion therapy for ARS

Sorption detoxification types, quite widely used today in medicine, are: (1) hemoperfusion (when blood is filtered through the column with activated carbon); (2) enterosorption—enteral use of oral adsorbents of a different type and (3) application-sorption therapy - use of carbon dressing for the healing of the burns and wounds.

The ground for use of direct perfusion of the blood through an adsorbent column for its purification (hemoperfusion) was the Kuzin A.M. Structural-Metabolic Theory in Radiobiology (1970) [29]. Organs and tissues exposed to ionizing radiation and radiomimetic influences are damaged by radiotoxins, which affect radiosensitive structures, and direct radiation-dependent changes in the macromolecules of the genome. Further investigations demonstrated that "radiotoxins" are reactive oxygen species (ROS) formed by water radiolysis. Oxidative stress causes DNA, protein and lipid oxidation and is responsible for the whole range of signs and syndromes of ARS [29]. Because of excessive lipid peroxidation, a lot of damaged cells appear that deepens the primary radiation injury repeatedly. In summary, ARS is a sum of primary damage due to oxidative stress plus so-called bystander effects [18], when cells exposed to ionizing radiation or radiomimetics can release signals that induce very similar effects on non-targeted neighboring cells.

Our first research of adsorptive therapy effects for acute radiation sickness (ARS) started in 1976 [30]. In this study, 69 inbred dogs were irradiated by external X-ray at the dose of 525 Rad (5.25 Gy). They were randomly assigned to three groups: first control group (n = 31), which received standard antibiotics therapy; second group (n = 19) got antibiotics + hemoperfusion 2 hours after irradiation and third group (n = 19) underwent saline infusion 4–5 hours after irradiation plus furosemide, and hemoperfusion 24 hours later. The results are presented in **Table 1**.

The highest survival rate was in the second group—68.4%, while in the control group, it was only 3.2%. Late hemoperfusion also resulted in a high survival rate—62.4%. Only 16% of an animal with hemoperfusion treatment (three dogs in each group) had critical leukopenia. In the control group, it was 93.5% of animals.

It is noteworthy, that mitotic index (a marker of the rate of cells division) (**Figure 1**) was significantly higher in the second group compared to the control one

Group	Survival rate, %	Animals with critical hematological indices, %		
		Bone marrow cellularity $<1.0 \times 10^9$/L	Leukopenia $<1.0 \times 10^9$/L	Thrombocytopenia, $<50.0 \times 10^9$/L
1 (n = 31)	3.2	13.4 ± 1.1	93.5	70
2 (n = 19)	68.4	17.0 ± 1.6	16.0	52.6
3 (n = 19)	62.4	16.6 ± 1.9	16.0	38.9

Table 1.
Hemoperfusion for ARS treatment [30].

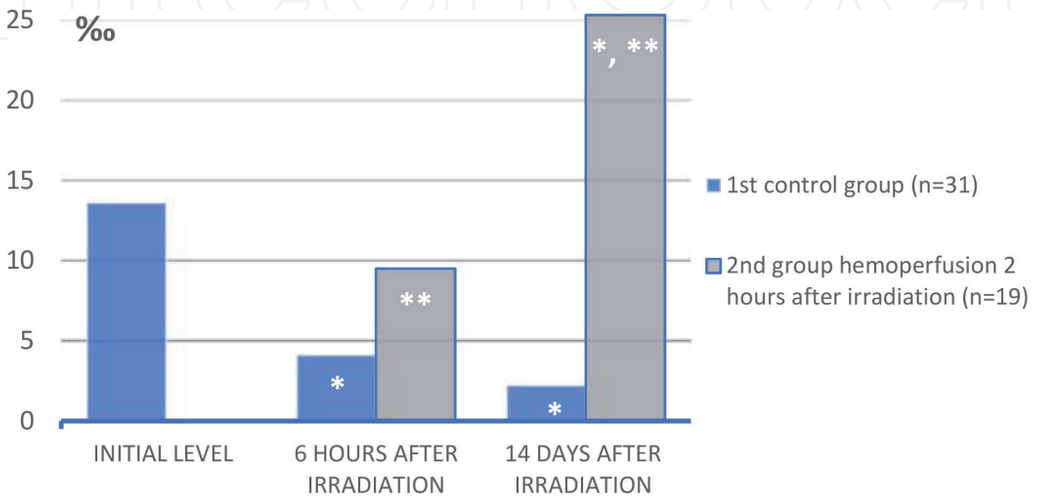

Figure 1.
*Mitotic index (‰) in the bone marrow of the dogs, exposed to external ionizing and hemoperfusion. Notes: * $p \leq 0.05$ compared to the initial level; ** $p \leq 0.05$ compared to the control group.*

(6 hours after irradiation) and even to the initial level (14th day after exposure to ionizing irradiation) [31].

Hemoperfusion with activated carbon also provided survival of 50% of dogs exposed to ionizing irradiation at the doses of 3.46 and 3.65 Gy [32]. These results were re-tested and developed within a special closed program of Research institutions of the Ministry of Health and the Ministry of Defense of USSR. Hemoperfusion methods were implemented into clinics [33, 34].

A team of researchers who carried out the experiment on dogs by irradiating them at the dose of 5.25 Gy, witnesses that perfusions of the blood through the column with a carbon adsorbent were quite short. Slugging of columns was the main reason for incomplete procedures (only 0.3-0.5 of circulating blood volume was purified) [35]. Despite these factors, the survival rate and other studied parameters were quite successful. We suppose that it could be explained by washout of dust particles from the surface of the adsorbent in the moment of primary contact with the blood, and viscosity changes inside the column after the replacement of rinsing solution to the blood also contributed to it. We think that positive secondary effects could be provided by nano- and microparticles (1–2 μ) of activated carbon, which contact with the blood. Their content is not controlled according to the standards of British (BP) and American (USP) Pharmacopeia.

Today, we have a lot of evidence that positive curative effects of carbon nanoparticles, alone or as a part of a composite, are obliged to their ability to scavenge the ROS and simulate suppose the effects of free oxygen radical scavenging enzymes. Sandhir R. et al. [36] believe that nanoantioxidants (inorganic nanoparticles possessing intrinsic antioxidant properties) would be more effective against

ROS-induced damage because they cross the blood-brain barrier. It is a potential application in treating and preventing neurodegenerative conditions [36]. Arifa R.D. et al. research demonstrated that nanocomposite with fullerol decreases the intensity of irinotecan-induced leukopenia and gastrointestinal damage in mice and do not diminish the tumoricidal effects of the drug [37]. The aftertreatment with the same nanocomposite ameliorates the graft-versus-host disease reactions in mice and reduces intestinal lesions and bacterial translocation; prevents mortality and morbidity [38]. Nano-fullerenes promote osteogenesis of human adipose-derived stem cells and possess a great antioxidant capacity [39].

Encouraging results have been found concerning the amelioration of side effects of one more radiomimetic—anthracycline antibiotic doxorubicin (DOX), which also is known by its ability to cause oxidative stress and leukopenia. Fullerenol $C_{60}(OH)_{24}$ nanoparticles improved the myocardial morphology of DOX-treated animals, but cause a certain degree of parenchymal degeneration by itself [40]. Such and similar cases [41] evidence the need for designing and searching for the nanocomposites with specific features, which will possess antioxidant capacity without notable cytotoxicity. One of the solutions could be the conjugation of carbon nanomaterials with albumin [42]. It was found that $C_{60}(OH)_{24}$ decreases the consequences of DOX-induced excessive oxidation in the tissues of kidneys, testis and lungs in mice [43]. An aqueous solution of fullerenol was quite effective to fight experimental arthritis in rats [44]. Andrievsky G.V. et al. demonstrated significant (but only by 15%) radioprotective properties of hydrate C_{60} fullerene in X-ray irradiation of the mice at the lethal dose of 7 Gy [45]. Water-soluble polyvinilpyrroli done-wrapped fullerene derivative showed to significantly inhibit UVA-promoted melanogenesis in normal human epidermis melanocytes and human melanoma HMV-II cells within a non-cytotoxicity dose range [46]. Huq R. et al. showed that nontoxic poly(ethylene glycol)-functionalized hydrophilic carbon clusters, known scavengers of the ROS superoxide and hydroxyl radical, are preferentially internalized by T lymphocytes over other splenic immune cells [47]. It was successfully used to reduce T-lymphocyte-mediated inflammation in experimental autoimmune encephalomyelitis (an animal model of multiple sclerosis) [47].

Another type of carbon material—carboxylated nanodiamonds, diminish the biochemical and histological signs of damage of γ-irradiated human erythrocytes [48]. On the other hand, hydrogenated nanodiamonds dramatically increase the sensitivity to radiation effects of human radioresistant cancer cell lines [49]. The same effect was seen considering the radiomimetic neocarcinostatin. Single-walled carbon nanotubes were found to be the efficient nanocarriers for drug delivery in the murine model of breast cancer [50, 51]. The team of researchers [52] synthesized the magnetic particles Fe_3O_4 in the shell from partially graphitized carbon and demonstrated their high intrinsic peroxidase-like catalytic activity, which promotes oxidative stress in human prostate cancer PC-3 cells in the presence of ascorbic acid. One more interesting study with a composite system of reduced graphene oxide—iron oxide nanoparticles showed that such a combination can synergistically induce physical and chemical damage to methicillin-resistant *Staphylococcus aureus* (MRSA) [53].

We must notice, that carbon nanoparticles possess great antioxidant properties and could be perspective for designing the nanopharmaceutical means and drugs to treat the disorders, when oxidative stress is an intrinsic part of pathogenesis, for leukopenia also. It means that further studies of carbon micro- and nanoparticles effects at parenteral routes of administration could finalize the discovery of quite a new method of mass treatment of acute radiation sickness.

Recently, several detailed reviews have been published on the pharmacological potential and prospects for the therapeutic use of cerium nanoparticles as traps of highly reactive oxygen (ROS) and nitrogen species (RNS) [54–56]. These reviews

are based on a variety of experimental studies both *in vitro* and *in vivo*. Not less interesting results for use of nanocrystal cerium dioxide (CeO_2) on the model of DOX-induced cardiomyopathy in rats we got [57]. Cardiomyocytes mostly are damaged because of the radiomimetic impact of the drug, and the violation of blood components was quite similar to the effects of ionizing irradiation. It is known that oxidative stress is an intrinsic part of the cytotoxic effects of DOX, and heart tissues are vulnerable because of a lack of intracellular antioxidant defense factors compared to other organs and systems [58].

In this study, we used 21 female white mongrel rats, which were randomly assigned to the next groups (n = 7): first control groups got weekly intraperitoneal (IP) injection of saline; rats of second (DOX) and third groups got three times a week IP injections of doxorubicin at a dose of 2.5 mg/kg (n = 7); rats of third (DOX + CeO_2) group got twice weekly IP injections of nanodisperse CeO_2 (0.2 mg/kg) next day after doxorubicin injections additionally. Treatments lasted for 2 weeks (**Figure 2**).

Injections of nanodisperse CeO_2 caused positive changes in myocardium structure. We observed improvement of a structure, decreased vacuolization of sarcoplasm, a number of cells with nuclei pathology was much lower (**Figure 4**) compared to the second group (**Figure 3**). A part of myocardium cells still had pyknotic nuclei with karyolysis signs. But mostly, the intensity of dystrophy and necrosis reduced and nuclei acquired oval shape again.

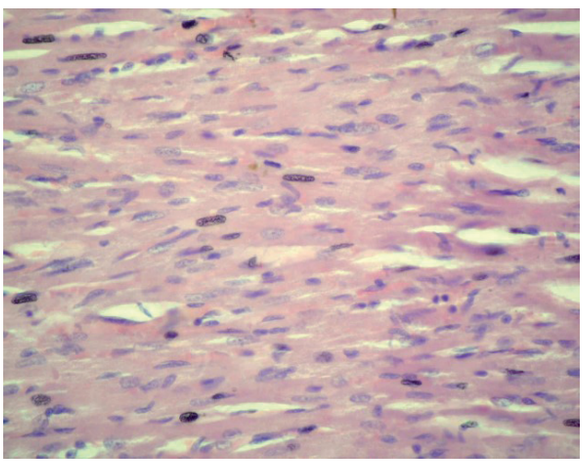

Figure 2.
Myocardium tissue of rat of the control group. H&E. ×600.

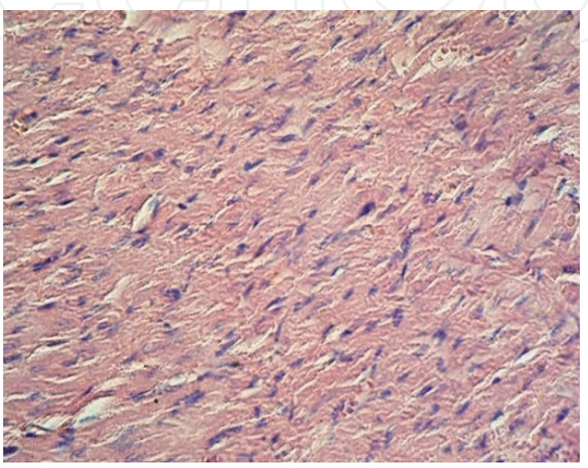

Figure 3.
Myocardium tissue of rat of the DOX group. H&E. ×600.

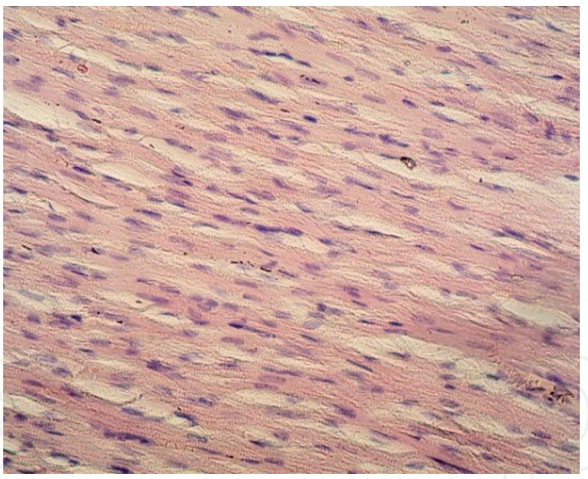

Figure 4.
Myocardium tissue of rat of the DOX + CeO_2 group. H&E. ×600.

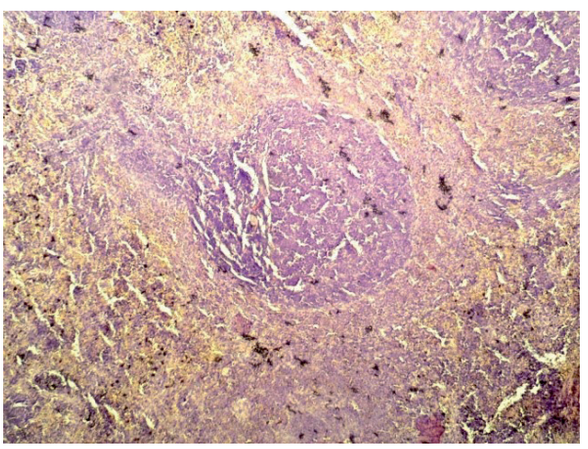

Figure 5.
Spleen structure of rat of the control group. H&E. ×600.

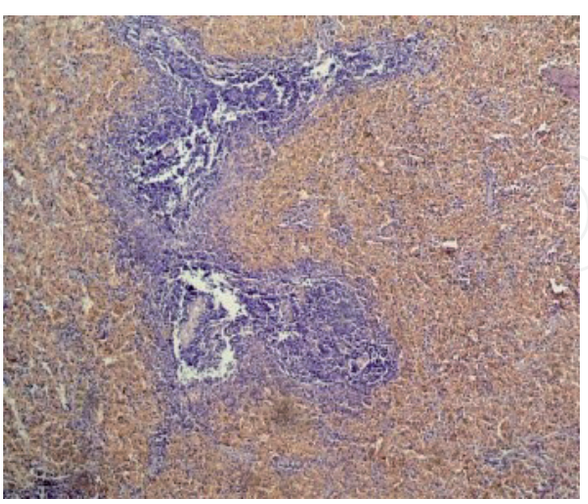

Figure 6.
Spleen structure of rat of the DOX group. H&E. ×600.

Also, we observed an increased number of lymphoid follicles in the spleen, which restored a circle-like shape (**Figures 5**–**7**).

There were no significant positive changes in the structure of liver parenchyma. We may just note restoring nuclei sizes and shape and a little bit lighter pale pink

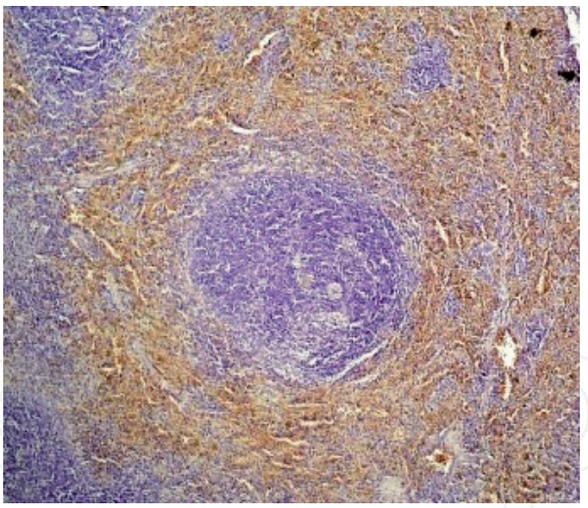

Figure 7.
Spleen structure of rat of the DOX + CeO2 group. H&E. ×600.

color of cytoplasm. It witnesses that the synthetic function of the liver was partly restored. Concerning the kidneys, no positive changes had been found.

Biochemical indices of lipid and protein peroxidation, antioxidant defense system showed that CeO_2 increased the activity of catalase by 24.6%, raised the level of reduced glutathione by 10.9% and decreased the level of oxidative modification of protein and lipids by 28.1 and 23.6%, respectively (compared to the group with untreated DOX-induced cardiomyopathy).

Bakht M.K. et al. proposed to reduce the actual radiation burden in patients exposed to radioisotope studies by arranging radiolabels for cerium oxide [59], and Colon J. et al. could achieve a good prophylactic result for radiation pneumonitis in mice that received nanocrystalline dioxide Ce [60]. One more fact should be mentioned here: because of bone marrow suppression and leukopenia development, lungs are fragile to injury by ionizing irradiation. They have their own host defense system, based on alveolar macrophages. Because of leukocytes toxic damage (by ionizing injury or radiation therapy or as the side effects of anti-cancer chemotherapy), resting macrophages can no longer be transformed which lead to radiation pneumonitis [24]. Heslet L. et al. showed that systemic administration of myelo stimulative cytokines was not helpful to prevent it because they do not penetrate the alveoli. That is why we suggest that oral adsorbents and/or parenteral use of CeO_2 (it penetrated the alveoli and prevents radiation pneumonitis on mice model) will enhance the prophylaxis and treatment of ARS and decrease the intensity of side effects of radiation therapy and cytostatic drugs.

4. Local signs of whole-body irradiation and efficacy of application-sorption therapy

External exposure to ionizing irradiation frequently results in radiation burns of the skin. Leukopenia just deepens the injury because of oppressing the regeneration processes. A retrospective report on injuries caused by the atomic bombing of Hiroshima showed that up to 65% of all type of injuries were "radiation-combined injury," when ionizing irradiation was coupled with burns, wounds and infections [61]. Regarding these facts and negative contribution of leukopenia also, we want to demonstrate the efficiency of activated carbon. The remarkable result was observed on the model of the thermal non-full depth burn in Albino rats [62]. The early application (within first

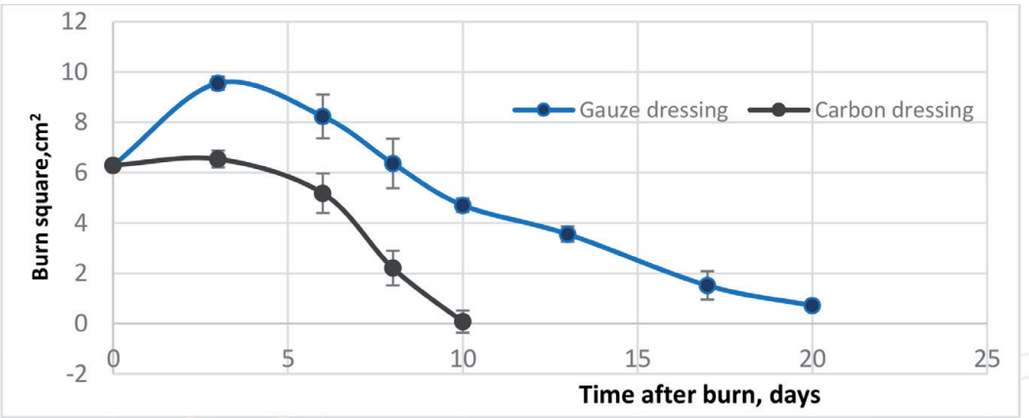

Figure 8.
The dynamics of healing of the non-full depth burn after application of the gauze and carbon dressing.

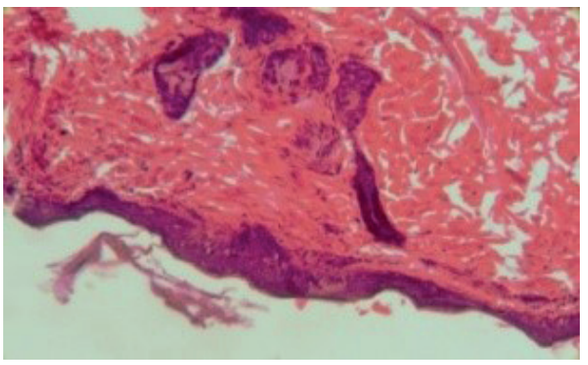

Figure 9.
Morphological structure of normal skin. H&E. ×200.

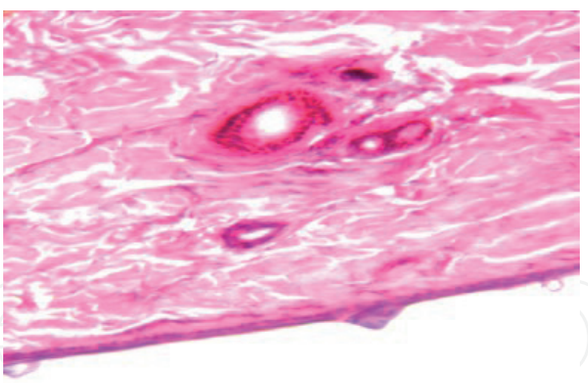

Figure 10.
Morphological structure of burned skin after use of gauze dressing on the 7th day after the thermal non-full depth burn. H&E. ×200.

60 min) of the highly active carbon fabrics (S_{BET} > 2000 m^2/g) twofold reduced the healing time: 10.80 ± 1.27 and 20.60 ± 0.86 days for adsorptive carbon and gauze dressings use, respectively (**Figure 8**).

Histological analysis demonstrated that adsoptive carbon dressings' application promoted the restoration of skin structure on the 7th day after injury in rats with the non-full burn (**Figures 9–11**).

Similar results were observed on the burns caused by external irradiation at the dose of 8 Gy. Epithelialization of burn wounds has been completed on 21.1 ± 4.1 versus 27.3 ± 5.7 days after trauma for carbon and gauze dressings use, respectively. One

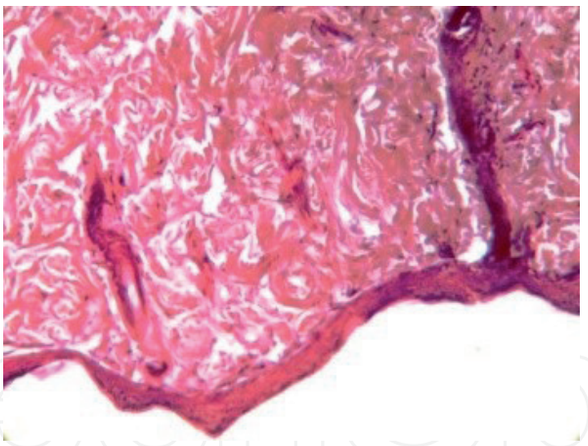

Figure 11.
Morphological structure of the burned skin after use of carbon dressing on the 7th day after the thermal non-full depth burn. H&E. ×200.

more fact relates to the treatment ultraviolet radiation-induced burns. Application of adsorptive carbon dressings significantly (by 1.5–1.7 times) accelerated the burn-healing time. All these data will be published soon.

These results presented the undoubted perspective for use of high capacity carbon fabrics for the treatment of superficial skin lesions, especially complicated by concomitant leukopenia.

5. Enterosorption for leukopenia management

Hemoperfusion as a procedure requires well-trained staff, specific equipment and sterility. It means that such method of sorption detoxification is not adapted to emergency exposure situations, during war-time and large human contingent injury. That is why the use of enteral sorption therapy (ingestion of activated carbon) is a more prospective method for such situations. Among the early studies, the great results were observed in the patients with lymphogranulomatosis undergoing radiotherapy [63], who were treated with fibrous carbon oral adsorbent. Enterosorption treatment allowed to continue planned schemes of radiation therapy and was more efficient than conventional methods for leukopenia healing. In the next study [64], cyclophosphane was given to Guerin tumor-grafted rats at the dose of 100 mg/kg of body weight on 10th and 13th days after tumor transplantation; enterosorption with synthetic SCN carbons (bulk density 0.3–0.4 g/cm^3) was administered next day after cyclophosphane injection. These expressed myeloprotective effects we approved and confirmed in the clinic. One more radiomimetic anti-cancer agent cisplatin was used in an experiment on Guerin tumor-grafted rats [65] and highly activated fibrous carbon material Carboline (Ukraine) successfully ameliorated a wide range of its side effects. Carboline is used in clinical practice also and demonstrates promising results [66].

Our latest experiments on rats exposed to X-ray irradiation in a total dose of 6 Gy (63 Rad per min, t = 11 min) demonstrated great results of novel oral carbon adsorbents administration to ameliorate radiation-caused leukopenia. We used two granulated activated carbons (AC) with a diameter of granules (0.25–0.5 mm) and bulk density 0.1 and 0.2 g/cm^3 (ES1 and ES2, respectively). Enterosorbents were administrated as radioprotectors, radiomitigators and therapeutic agents (at the dose of 10 ml/kg, admixed to the food, three days before and nine days after ionizing irradiation exposure). Irradiation caused a 10-fold decrease in the white blood

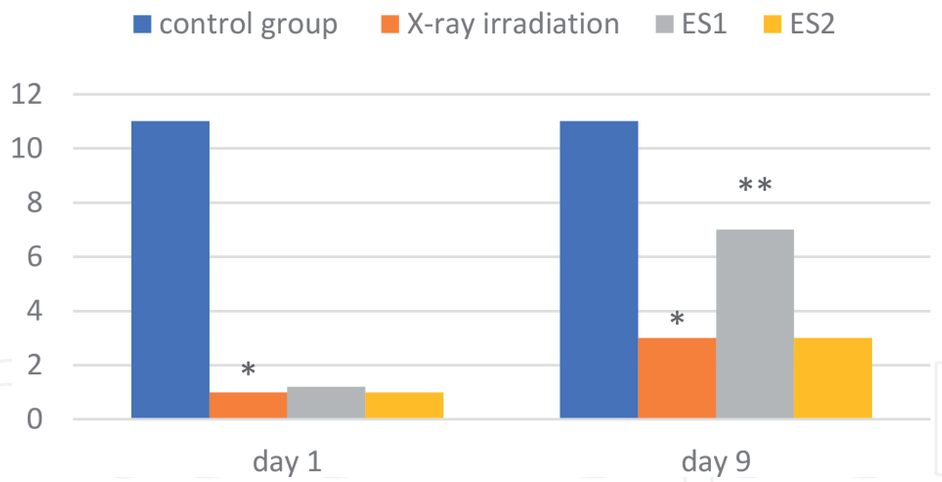

Figure 12.
*White blood cells count (10^9/L) in X-ray irradiation at the dose of 6 Gy and oral adsorbents administration. Notes: $p < 0.05$ compared to: *—the control group, **—X-ray irradiation group.*

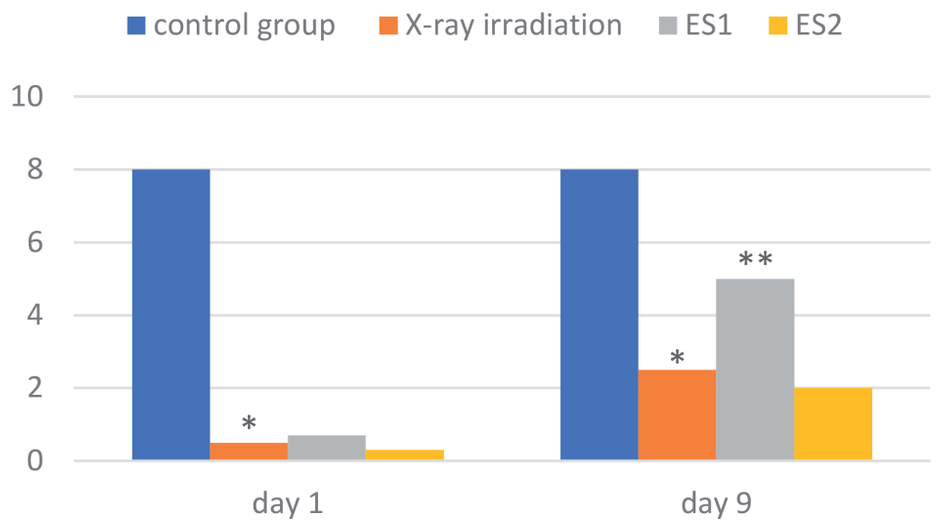

Figure 13.
*Lymphocytes count (10^9/L) in X-ray irradiation at the dose of 6 Gy and oral adsorbents administration. Notes. $p < 0.05$ compared to: *—the control group, **—X-ray irradiation group.*

cells count. ES1 administration raised the index twice on the 9th day after X-ray exposure, while ES2 produced fewer results (**Figure 12**).

The same effect was observed concerning the lymphocytes count (**Figure 13**). Structural differences among those two carbon adsorbents are estimated. These results will be published soon in detail.

So, as we observed, specific oral adsorbents with specified porosity and pores distribution are quite successful to fight the iatrogenic leukopenia because of the influence of ARS or anti-cancer treatment.

Oral carbon materials have a high capability to decrease the emesis caused by anti-cancer treatment [66, 67]. Also, it is a unique mean with anti-diarrhea action, which could be implemented in the clinics for the treatment of ARS-induced gastrointestinal subsyndrome as well as for dyspepsia syndrome caused by tumoricidal therapy.

Thus, enterosorption for the results on the animal study and use in clinics do prevent hematotoxicity of anti-cancer treatment and significantly ameliorated leukopenia and its consequences.

6. Oral carbon adsorbents as an addition to classical treatment of leukopenia with G-CSF

Abovementioned positive results led us to design of a new improved version of carbon oral adsorbent, which was used in early experiments [64, 68]. An old prototype C1 and his new version C2 were approved on the model of melphalan-induced bone marrow suppression [69–71]. We demonstrated that myeloprotective action of carbon granulated enterosorbent C1 (bulk density of 0.28 g/cm^3, specific surface of 1719 m^2/g and mesopore area of 239 m^2/g) is significantly less compared to effects of adsorbent C2 with bulk density of 0.18 g/cm^3, total specific surface of 2162 m^2/g and mesopore area of 565 m^2/g (**Figure 14**).

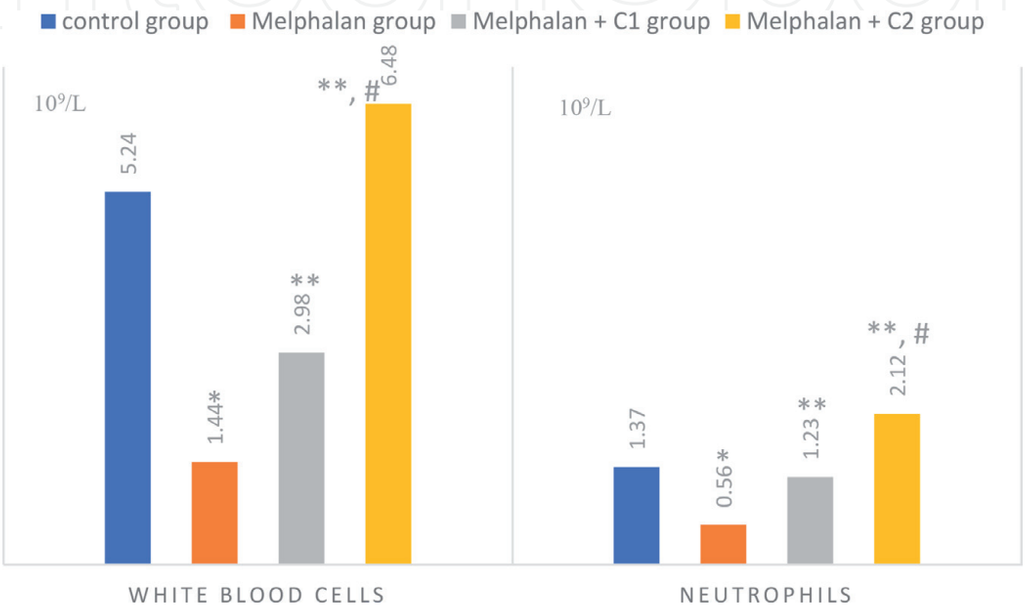

Figure 14.
*White blood cells and neutrophils counts (10^9/L) on the 8th day after melphalan injection at the dose of 3 mg/kg and administration of oral carbon adsorbents C1 and C2 in a study on rats. Notes. *—p < 0.05 compared to the control group; **—p < 0.05 compared to the melphalan group; #—p < 0.05 and compared to the Melphalan + C1group.*

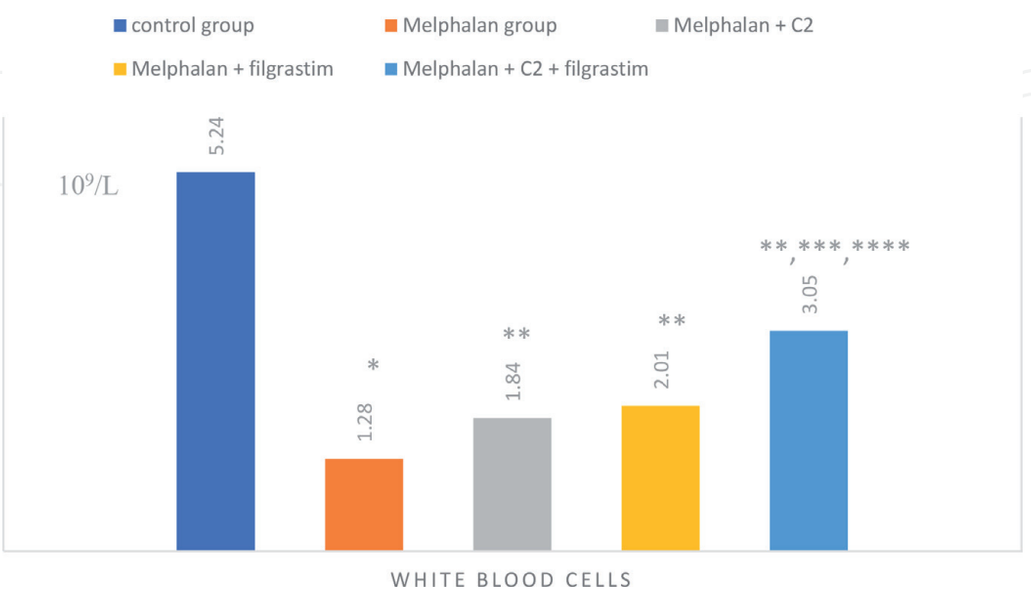

Figure 15.
*White blood cells count (10^9/L) on the 8th day after melphalan injection at the dose of 4 mg/kg and administration of oral carbon adsorbent and filgrastim in the study on rats. Notes. p < 0.05 compared to: *—Control group; **—Melphalan group; ***—Melphalan + C2 group; ****—Melphalan + filgrastim group.*

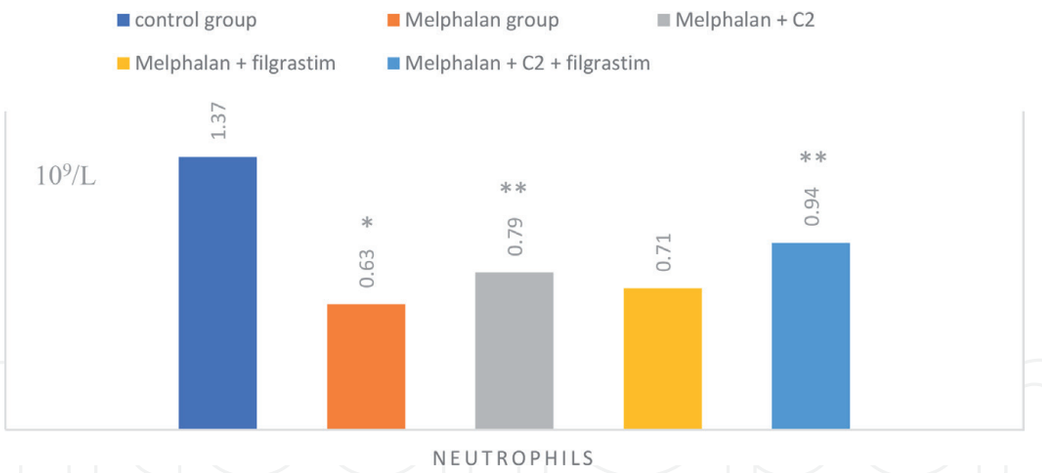

Figure 16.
*Neutrophils count (10^9/L) on the 8th day after melphalan injection at the dose of 4 mg/kg and administration of oral carbon adsorbent and filgrastim in a study on rats. Notes. $p < 0.05$ compared to: *—Control group; **—Melphalan group.*

C2 enterosorbent administration normalized the prooxidant/antioxidant system indices too [71]. Oxidative stress is an intrinsic part of ionizing radiation and radiomimetic injury, and enteral sorption therapy possesses notable antioxidant effects.

Adding the carbon oral adsorbent to classical scheme for the treatment of leukopenia with G-CSF (caused by single intravenous melphalan injection at the dose of 4 mg/kg) demonstrated significant myeloprotective effect and synergy compared to single-use effects of each agent alone [70] (**Figures 15** and **16**). C2 and filgrastim combination caused increase of white blood cells count by 138.3% compared to the melphalan group; by 65.8% compared to melphalan + C2 group, and by 51.7% compared to use of filgrastim alone.

We must note that in this study, we got an unexpected significant increase of platelets level from (254.60 ± 45.59) to (505.40 ± 70.68) × 10^9/L in a group of rats that received the combined treatment with oral adsorbent and G-CSF. Isolated administration of enterosorbent C2 tended to raise the level of thrombocytes, we suppose because of general detoxification action.

Use of enterosorbent or combined use of both preparations provided significantly better effects toward the prooxidant/antioxidant balance in rats.

The important issue is that combination of G-CSF and carbon adsorbents [69] as well as enteral sorption therapy use alone [65] does not affect the efficacy of anticancer treatment; we proved it by our experiments on Guerin tumor-grafted rats.

7. Conclusions

Leukopenia is an essential part of the damage caused by ionizing irradiation and/or radiomimetic influences (as tumoricidal chemotherapy). Leukocytes play an important role in immune defense, tissue regeneration, the functioning of the main organs and systems; and the degree of bone marrow suppression determines the survival of victims in ionizing radiation exposure as well as the efficacy of anticancer chemotherapy. All three methods of sorption detoxification with activated carbons such as hemoperfusion (when blood is filtered through the column with activated carbon); enterosorption—peroral use of oral adsorbents and application-sorption therapy (use of carbon dressing for the healing of the burns and wounds), can be successfully used for the leukopenia prophylaxis and treatment in ionizing irradiation exposure, side effects of anti-cancer chemotherapy, as well as for the boosting of healing of associated skin damage.

Enterosorption demonstrates significant synergy with hemopoietic cytokines in the treatment of bone marrow suppression caused by such an aggressive agent as melphalan (a derivative of mustard nitrogen). Nanocrystal cerium dioxide could be useful for oxidative stress modulation caused by such radiomimetic as anti-cancer anthracycline antibiotic doxorubicin. Modification of pathological biochemical processes which provoke bone marrow suppression and leukopenia is a basis of the efficacy of sorption detoxification in acute radiation syndrome as well as to decrease the side effects of anti-cancer chemotherapy. Our findings may contribute to the refinement of current risk stratification algorithms for acute radiation sickness treatment.

Conflict of interest

The authors declare the absence of the conflict of interest.

Abbreviations

NPP	nuclear power plants
ARS	acute radiation sickness.
G-CSF	granulocyte colony-stimulating factor.
ROS	reactive oxygen species.
Gy	gray, unit of ionizing radiation dose.

Author details

Oksana O. Shevchuk[1*], Elisaveta A. Snezhkova[2], Anatoliy G. Bilous[3], Veronika V. Sarnatskaya[2], Kvitoslava I. Badakhivska[2], Larysa A. Sakhno[2], Vasyl F. Chekhun[2] and Volodymyr G. Nikolaev[2]

1 I. Horbachevsky Ternopil State Medical University, Ternopil, Ukraine

2 R.E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology of National Academy of Science of Ukraine, Kyiv, Ukraine

3 Institute of General and Inorganic Chemistry of National Academy of Science of Ukraine, Kyiv, Ukraine

*Address all correspondence to: shevchukoo@tdmu.edu.ua

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References

[1] Davis S, Day RW, Kopecky KJ, Mahoney MC, McCarthy PL, Michalek AM, et al. Childhood leukaemia in Belarus, Russia, and Ukraine following the Chernobyl power station accident: Results from an international collaborative population-based case—Control study. International Journal of Epidemiology. 2006;**35**:386-396. DOI: 10.1093/ije/dyi220

[2] Mettler FA, Gus'kova AK, Gusev I. Health effects in those with acute radiation sickness from the Chernobyl accident. Health Physics. 2007;**93**:462-469. DOI: 10.1097/01.HP.0000278843.27969.74

[3] Belyi D, Kovalenko A, Bazyka D, Bebeshko V. Non-cancer effects in acute radiation syndrome survivors in Ukraine. Health Physics. 2010;**98**:876-884. DOI: 10.1097/HP.0b013e3181d270e4

[4] Hayano RS, Tsubokura M, Miyazaki M, Satou H, Sato K, Masaki S, et al. Internal radiocesium contamination of adults and children in Fukushima 7 to 20 months after the Fukushima NPP accident as measured by extensive whole-body-counter surveys. Proceedings of the Japan Academy. Series B. 2013;**89**:157-163. DOI: 10.2183/pjab.89.157

[5] Kobayashi T, Nagai H, Chino M, Kawamura H. Source term estimation of atmospheric release due to the Fukushima Dai-ichi nuclear power plant accident by atmospheric and oceanic dispersion simulations. Journal of Nuclear Science and Technology. 2013;**50**:255-264. DOI: 10.1080/00223131.2013.772449

[6] Parakkal D, Ehrenpreis ED. Medical management of radiation effects on the intestines. Radiation Therapy for Pelvic Malignancy and its Consequences. New York, NY: Springer New York; 2015. DOI:10.1007/978-1-4939-2217-8_15

[7] Shadad AK, Sullivan FJ, Martin JD, Egan LJ. Gastrointestinal radiation injury: Prevention and treatment. World Journal of Gastroenterology. 2013;**19**:199-208

[8] Teo MTW, Sebag-Montefiore D, Donnellan CF. Prevention and management of radiation-induced late gastrointestinal toxicity. Clinical Oncology. 2015;**27**:656-667. DOI: 10.1016/j.clon.2015.06.010

[9] WHO. Ionizing radiation, health effects and protective measures. Fact Sheet; 2016

[10] Bartelink H, Roelofsen F, Eschwege F, Rougier P, Bosset JF, Gonzalez DG, et al. Concomitant radiotherapy and chemotherapy is superior to radiotherapy alone in the treatment of locally advanced anal cancer: Results of a phase III randomized trial of the European organization for research and treatment of cancer radiotherapy and gastro. Journal of Clinical Oncology. 1997;**15**:2040-2049. DOI: 10.1200/JCO.1997.15.5.2040

[11] D'Amico AV, Whittington R, Bruce Malkowicz S, Schultz D, Blank K, Broderick GA, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. Journal of the American Medical Association. 1998;**280**:969-974. DOI: 10.1001/jama.280.11.969

[12] Nagata Y, Takayama K, Matsuo Y, Norihisa Y, Mizowaki T, Sakamoto T, et al. Clinical outcomes of a phase I/II study of 48 Gy of stereotactic body radiotherapy in 4 fractions for primary lung cancer using a stereotactic body frame. International Journal of Radiation Oncology, Biology, Physics. 2005;**63**:1427-1431. DOI: 10.1016/j.ijrobp.2005.05.034

[13] Liu W, Zhang C-C, Li K. Prognostic value of chemotherapy-induced leukopenia in small-cell lung cancer. Cancer Biology and Medicine. 2013;**10**:92-98. DOI: 10.7497/j.issn.2095-3941.2013.02.005

[14] Xing C, Liang B, Wu J, Yang Q, Hu G, Yan Y, et al. Prognostic significance of leukopenia during the induction phase in adult B cell acute lymphoblastic leukemia. Cancer Management and Research. 2018;**10**: 625-635. DOI: 10.2147/CMAR.S158359

[15] Management of Terrorist Events Involving Radioactive Material. NCRP report No. 138; Bethesda; 2001

[16] López M, Martín M. Medical management of the acute radiation syndrome. Reports of Practical Oncology & Radiotherapy. 2011;**16**:138-146. DOI: 10.1016/j.rpor.2011.05.001

[17] Popov D, Jones J, Maliev V. Radiation toxins—Effects of radiation toxicity, molecular mechanisms of action, radiomimetic properties and possible countermeasures for radiation injury. In: Current Topics in Ionizing Radiation Research. Rijeka, Croatia: InTech; 2012. pp. 215-242. DOI: 10.5772/33806

[18] Rzeszowska-Wolny J, Przybyszewski WM, Widel M. Ionizing radiation-induced bystander effects, potential targets for modulation of radiotherapy. European Journal of Pharmacology. 2009;**625**:156-164. DOI: 10.1016/j.ejphar.2009.07.028

[19] Dainiak N. Medical management of acute radiation syndrome and associated infections in a high-casualty incident. Journal of Radiation Research. 2018;**59**:ii54-ii64. DOI: 10.1093/jrr/rry004

[20] Povirk LF. DNA damage and mutagenesis by radiomimetic DNA-cleaving agents: Bleomycin, neocarzinostatin and other enediynes. Mutation Research. 1996;**355**:71-89

[21] Hauer-Jensen M, Kumar KS, Wang J, Berbee M, Fu Q, Marjan B. Intestinal toxicity in radiation—And combined injury: Significance, mechanisms, and countermeasures. In: Global Terrorism Issues and Developments. Hauppauge (NY): Nova Science Publishers; 2008. pp. 61-100

[22] Levis AG, Spanio L, De Nadai A. Radiomimetic effects of a nitrogen mustard on survival, growth, protein and nucleic acid synthesis of mammalian cells in vitro. Experimental Cell Research. 1963;**31**:19-30. DOI: 10.1016/0014-4827(63)90151-4

[23] Waselenko JK, MacVittie TJ, Blakely WF, Pesik N, Wiley AL, Dickerson WE, et al. Medical management of the acute radiation syndrome: Recommendations of the strategic national stockpile radiation working group. Annals of Internal Medicine. 2004;**140**:1037. DOI: 10.7326/0003-4819-140-12-200406150-00015

[24] Heslet L, Bay C, Nepper-Christensen S. Acute radiation syndrome (ARS)—Treatment of the reduced host defense. International Journal of General Medicine. 2012;**5**:105-115. DOI: 10.2147/IJGM.S22177

[25] Aapro MS, Bohlius J, Cameron DA, Lago LD, Donnelly JP, Kearney N, et al. 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. European Journal of Cancer. 2011;**47**:8-32. DOI: 10.1016/j.ejca.2010.10.013

[26] Schwenkglenks M, Pettengell R, Jackisch C, Paridaens R, Constenla M, Bosly A, et al. Risk factors for chemotherapy-induced neutropenia occurrence in breast cancer patients: Data from the INC-EU prospective

observational European neutropenia study. Support Care Cancer. 2011;**19**:483-490. DOI: 10.1007/s00520-010-0840-y

[27] Barnes G, Pathak A, Schwartzberg L. Pharmacoeconomics of granulocyte colony-stimulating factor: A critical review. Advances in Therapy. 2014;**31**:683-695. DOI: 10.1007/s12325-014-0133-9

[28] Singh VK, Newman VL, Seed TM. Colony-stimulating factors for the treatment of the hematopoietic component of the acute radiation syndrome (H-ARS): A review. Cytokine. 2015;**71**:22-37

[29] Kuzin AM. Structural-Metabolic Theory in Radiobiology. Moscow: Nauka; 1970

[30] Nikolaev VG, Pinchuk LB, Umansky MA, Pinchuk VG, Burushkina TN, Petrenko SV, et al. Early experimental studies on hemoperfusion as a treatment modality for acute radiation disease. Artificail Organs. 1993;**17**:362-368

[31] Nikolaev VG. Sorption therapy with the use of activated carbons: Effects on regeneration of organs and tissues, hemoperfusion, plasmaperfusion and other clinical uses of general, biospecific, immuno and leucocyte Adsorbents. Singapore: World Scientific Publishing Co Pte Ltd.; April 2017. p. 221-243. doi:10.1142/9789814749084_0007.

[32] Chertkov KS, Andrianova IY, Andrushchenko VN, Vernigorova LA. Experimental development of combined treatment for acute radiation sickness. In: Horn B, editor. 9th Int. Congr. of Int. Radiat. Prot. Assoc. Vienna, Austria: International Atomic Energy Agency (IAEA); 1996. pp. 129-131

[33] Chertkov KS, Andrianova IE, Andrushchenko VN, Vernigorova LA, Glushkov VA, Davydova SA, et al. Advances and prospects of a combined therapy of acute radiation injury in experiments. Radiatsionnaia Biologiia, Radioecologiia. 1999;**39**:563-567

[34] Vernigorov LA, Chertkov KS. Methodical Recommendations on the Use of Hemosorption in Clinical Conditions for Treatment of Acute Radiation Sickness. Moscow: Meditsina; 1983

[35] Nikolaev VG, Strelko VV. Method of Hemocarboperfusion in Experiments and in Clinics. Kyiv: Naukova Dumka; 1984

[36] Sandhir R, Yadav A, Sunkaria A, Singhal N. Nano-antioxidants: An emerging strategy for intervention against neurodegenerative conditions. Neurochemistry International. 2015;**89**:209-226. DOI: 10.1016/j.neuint.2015.08.011

[37] Arifa RDN, De Paula TP, Madeira MFM, Lima RL, Garcia ZM, Ávila TV, et al. The reduction of oxidative stress by nanocomposite Fullerol decreases mucositis severity and reverts leukopenia induced by Irinotecan. Pharmacological Research. 2016;**107**:102-110. DOI: 10.1016/j.phrs.2016.03.004

[38] Bernardes PTT, Rezende BM, Resende CB, De Paula TP, Reis AC, Gonçalves WA, et al. Nanocomposite treatment reduces disease and lethality in a murine model of acute graft-versus-host disease and preserves anti-tumor effects. PLoS One. 2015;**10**:e0123004. DOI: 10.1371/journal.pone.0123004

[39] Yang X, Li C-J, Wan Y, Smith P, Shang G, Cui Q. Antioxidative fullerol promotes osteogenesis of human adipose-derived stem cells. International Journal of Nanomedicine. 2014;**9**:4023-4031. DOI: 10.2147/IJN.S66785

[40] Borović ML, Ičević I, Kanački Z, Žikić D, Seke M, Injac R, et al. Effects

of Fullerenol $C_{60}(OH)_{24}$ nanoparticles on a single-dose doxorubicin-induced cardiotoxicity in pigs: An ultrastructural study. Ultrastructural Pathology. 2014;**38**:150-163. DOI: 10.3109/01913123.2013.822045

[41] Injac R, Prijatelj M, Strukelj B. Fullerenol nanoparticles: Toxicity and antioxidant activity. In: Methods Molecular Biology Oxidative Stress Nanotechnology. Totowa, NJ: Humana Press; 2013. pp. 75-100. DOI: 10.1007/978-1-62703-475-3_5

[42] Liu Y, Ge Y-S, Jiang F-L, Xu Z-Q, Zhang M-F. Binding of fullerol to human serum albumin: Spectroscopic and electrochemical approach. Journal of Photochemistry and Photobiology B: Biology. 2011;**108**:34-43. DOI: 10.1016/j.jphotobiol.2011.12.006

[43] Srdjenovic B, Milic-Torres V, Grujic N, Stankov K, Djordjevic A, Vasovic V. Antioxidant properties of fullerenol $C_{60}(OH)_{24}$ in rat kidneys, testes, and lungs treated with doxorubicin. Toxicology Mechanisms and Methods. 2010;**20**:298-305. DOI: 10.3109/15376516.2010.485622

[44] Yudoh K, Karasawa R, Masuko K, Kato T. Water-soluble fullerene (C60) inhibits the development of arthritis in the rat model of arthritis. International Journal of Nanomedicine. 2009;**4**:217-225

[45] Andrievsky GV, Bruskov VI, Tykhomyrov AA, Gudkov SV. Peculiarities of the antioxidant and radioprotective effects of hydrated C60 fullerene nanostuctures in vitro and in vivo. Free Radical Biology & Medicine. 2009;**47**:786-793. DOI: 10.1016/J.FREERADBIOMED.2009.06.016

[46] Xiao L, Matsubayashi K, Miwa N. Inhibitory effect of the water-soluble polymer-wrapped derivative of fullerene on UVA-induced melanogenesis via downregulation of tyrosinase expression in human melanocytes and skin tissues. Archives of Dermatological Research. 2007;**299**:245-257. DOI: 10.1007/s00403-007-0740-2

[47] Huq R, Samuel ELG, Sikkema WKA, Nilewski LG, Lee T, Tanner MR, et al. Preferential uptake of antioxidant carbon nanoparticles by T lymphocytes for immunomodulation. Scientific Reports. 2016;**6**:33808. DOI: 10.1038/srep33808

[48] Santacruz-Gomez K, Silva-Campa E, Melendrez-Amavizca R, Teran Arce F, Mata-Haro V, Landon PB, et al. Carboxylated nanodiamonds inhibit γ-irradiation damage of human red blood cells. Nanoscale. 2016;**8**:7189-7196. DOI: 10.1039/C5NR06789H

[49] Grall R, Girard H, Saad L, Petit T, Gesset C, Combis-Schlumberger M, et al. Impairing the radioresistance of cancer cells by hydrogenated nanodiamonds. Biomaterials. 2015;**61**:290-298. DOI: 10.1016/J.BIOMATERIALS.2015.05.034

[50] Al Faraj A, Shaik AP, Shaik AS. Magnetic single-walled carbon nanotubes as efficient drug delivery nanocarriers in breast cancer murine model: Noninvasive monitoring using diffusion-weighted magnetic resonance imaging as sensitive imaging biomarker. International Journal of Nanomedicine. 2015;**10**:157-168. DOI: 10.2147/IJN.S75074

[51] Al Faraj A, Shaik AS, Al Sayed B. Preferential magnetic targeting of carbon nanotubes to cancer sites: Noninvasive tracking using MRI in a murine breast cancer model. Nanomedicine. 2015;**10**:931-948. DOI: 10.2217/nnm.14.145

[52] An Q, Sun C, Li D, Xu K, Guo J, Wang C. Peroxidase-like activity of Fe_3O_4@carbon nanoparticles enhances ascorbic acid-induced oxidative stress and selective damage to PC-3 prostate cancer cells. ACS Applied Materials &

Interfaces. 2013;**5**:13248-13257. DOI: 10.1021/am4042367

[53] Pan W-Y, Huang C-C, Lin T-T, Hu H-Y, Lin W-C, Li M-J, et al. Synergistic antibacterial effects of localized heat and oxidative stress caused by hydroxyl radicals mediated by graphene/iron oxide-based nanocomposites. Nanomedicine: Nanotechnology, Biology and Medicine. 2016;**12**:431-438. DOI: 10.1016/J.NANO.2015.11.014

[54] Celardo I, Pedersen JZ, Traversa E, Ghibelli L. Pharmacological potential of cerium oxide nanoparticles. Nanoscale. 2011;**3**:1411. DOI: 10.1039/c0nr00875c

[55] Das S, Dowding JM, Klump KE, McGinnis JF, Self W, Seal S. Cerium oxide nanoparticles: Applications and prospects in nanomedicine. Nanomedicine. 2013;**8**:1483-1508. DOI: 10.2217/nnm.13.133

[56] Walkey C, Das S, Seal S, Erlichman J, Heckman K, Ghibelli L, et al. Catalytic properties and biomedical applications of cerium oxide nanoparticles. Environmental Science. Nano. 2015;**2**:33-53. DOI: 10.1039/c4en00138a

[57] Khudenko NV, Sarnatska VV, Paziuk LM, Timashkov IP, Nikolaev VG. Experimental doxorubicin-induced cardiomyopathy: Effects of nanodisperse cerium dioxide. Experimental Oncology. 2019. In press

[58] Golubtsov OU, Tyrenko VV, Lutov VV, Maslyakov VV, Makiev RG. Cardiovascular complications of anticancer therapy. Modern problems of science and education. 2017;(2):1-15. (In Russian)

[59] Bakht MK, Hosseini V, Honarpisheh H. Radiolabeled nanoceria probes may reduce oxidative damages and risk of cancer: A hypothesis for radioisotope-based imaging procedures. Medical Hypotheses. 2013;**81**:1164-1168. DOI: 10.1016/j.mehy.2013.10.008

[60] Colon J, Herrera L, Smith J, Patil S, Komanski C, Kupelian P, et al. Protection from radiation-induced pneumonitis using cerium oxide nanoparticles. Nanomedicine: Nanotechnology, Biology and Medicine. 2009;**5**:225-231. DOI: 10.1016/j.nano.2008.10.003

[61] DiCarlo AL, Ramakrishnan N, Hatchett RJ. Radiation combined injury: Overview of NIAID research. Health Physics. 2010;**98**:863-867. DOI: 10.1097/HP.0b013e3181a6ee32

[62] Sakhno L, Yurchenko O, Sidorenko A, Dvorshchenko O, Maslenny V, Korotich V, et al. Application of adsorptive carbon dressing accelerates skin regeneration after the non-full depth burn. The International Journal of Artificial Organs. 2014;**37**:642

[63] Muravskaya GV, Nikolaev VG, Sergeev VP, Krutilina NI, Bonatskaya LV, Klevtsov VN, et al. Enterosorption in Oncotherapy. Artificial Cells, Blood Substitutes, and Immobilization Biotechnology. 1991;**19**:167-174. DOI: 10.3109/10731199109117823

[64] Bonatskaya LV, Plotnikov VM, Nikolaev VG. Decrease of hematotoxicity of anticancer preparation upon enterosorption. Experimental Oncology. 1989;**23**(11):71-73. (In Russian)

[65] Sakhno LA, Yurchenko OV, Maslenniy VN, Bardakhivskaya KI, Nikolaeva VV, Ivanyuk AA, et al. Enterosorption as a method to decrease the systemic toxicity of cisplatin. Experimental Oncology. 2013;**35**:45-52

[66] Nikolaev VG, Andreychin MA, Bardakhivskaya KI, Sakhno LA, Kopcha VS, Yushko LA, et al. Practical Recommendations on the Use of Granulated Carbon Enterosorbents "Carboline". Kyiv: DIA; 2013

[67] Ponomarova OV, Pivnyuk VM, Nosko MM, Sakhno LO, Dekhtiar TV,

Nikolaev VG, et al. Prophylaxis by coal enterosorbent of acute and extended emethogenic toxicity of cancer patient chemotherapy. Oncology. 2008;**3**: 370-373. (In Ukrainian)

[68] Bonatskaya LV, Zinevich AK. Enterosorption as a method of prophylaxis and treatment of some complication of cancer chemotherapy. In: Proceedings of the Conference Sorption Methods for Detoxification and Immune System Correction. Kharkiv; 1982. p. 4

[69] Shevchuk OO, Posokhova KA, Todor IN, Lukianova NY, Nikolaev VG, Chekhun VF. Prevention of myelosuppression by combined treatment with enterosorbent and granulocyte colony-stimulating factor. Experimental Oncology. 2015;**37**:135-138

[70] Shevchuk OO, Bodnar YY, Bardakhivska KI, Datsko TV, Volska AS, Posokhova KA, et al. Enterosorption combined with granulocyte colony stimulating factor decreases melphalan gonadal toxicity. Experimental Oncology. 2016;**38**:172-175

[71] Shevchuk OO, Posokhova KA, Sidorenko AS, Bardakhivska KI, Maslenny VM, Yushko LA, et al. The influence of enterosorption on some haematological and biochemical indices of the normal rats after single injection of melphalan. Experimental Oncology. 2014;**36**:94-100