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Analysis of Modern Pathomorphological Data Obtained in Experimental Studies

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Resume. It is known that the factors determining radiosensitivity are complex and depend on the type of laboratory animals, their age, constitution, state of metabolic processes, dose and type of radiation. It is generally accepted that there is a threshold dose for most somatic effects below which no significant effects are observed. By increasing the dose, the level of the body's reaction increases. The distribution of radiation effects over time is of great importance. Studies have shown that the reaction of the mammalian organism to radiation can be considered as a sum of interrelated effects on all their organs and processes. Different types of hematopoietic cells show different sensitivity - erythroblasts are more radiosensitive than myelocytes, myelocytes, megakaryocytes, etc. The radiation-protective properties of bee venom have been studied in various ways.

Keywords: electromagnetic vibrations, X-rays and γ-rays, flow of α- and β-particles (electrons), protons, positrons, neutrons.

The response of a living organism to radiation exposure is not manifested by isolated disturbances of functions and structures, but by a complex reaction of various functional systems. Among the integrated systems, the central and peripheral organs of blood formation have a special place, for example, in experimental animals that died from high-dose radiation with disturbances of homeostasis and internal organs incompatible with viability, some authors note minimal changes in peripheral blood. Some authors believe that lymphocytes in the peripheral blood are very sensitive to radiation, their content decreases sharply immediately after injuries. According to other data, lymphocytes do not have high radiosensitivity, their content increases significantly after radiation.

The effects on the blood system of rats were analyzed before and after total γ-irradiation. Intraperitoneal injection of bee venom at doses of 0.1 and 0.5 mg/kg before irradiation has been shown to have a radioprotective effect, which is reflected in the improvement of a number of hematological parameters. Bee venom in doses of 0.1 and 0.5 mg/kg used after irradiation alleviates the passing of moderate-weight TNBC, stimulates recovery processes in the blood system [Nikolaeva A.A., 2011].

Rozhdestvensky L.M. [2013] evaluated the antiradiation therapeutic and leukopoiesis-stimulating effects of recombinant human granulocyte colony-stimulating factor (GKSO)-leucostim and nepomax in large laboratory animals. In dogs, the total effect of γ-irradiation at a dose of 3 Gr for 7-24 days resulted in the development of mainly severe OCN. In similar experimental conditions, administration of leucostim to animals from day 1 to day 17-21 reduced the severity of TNA to mild in three and to moderate in one of five dogs (1 dog died of hemorrhagic syndrome). Leukostim had a restorative effect on leukopoiesis. In experiments on dogs irradiated with a dose of 3.5 g, nepomax administration for 3 weeks saved 4 out of 6 dogs in the main group from death against 2 out of 9 dogs in the control group. Administration of Neipomax reduced the severity of leukopenia/neutropenia in the acute phase of radiation sickness and promoted faster recovery of peripheral blood leukocyte/neutrophil counts. The obtained results corresponded to the data of other authors who used GKSO under similar experimental conditions.

In vitro experiments on the differentiation of human mesenchymal stem cells (MSCs) into progenitor-cell hematopoietic stem cells (GOS) and endothelial cells have shown that MOS have hematopoietic potential by changing their morphology and gene expression profile. Targeted MO'H was administered intravenously to lethally irradiated mice. Long-term survival of recipients was determined by restoration of hematopoiesis after transplantation of MOH alone, without the contribution of GOH. Polymerase chain reaction (PCR) analysis of chimerism detected targeted cells in the peripheral blood immediately after injection and in the lungs 24 hours later. But in late stages, no donor cells were found in any of the tissues studied. Despite the

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loss of donor cells, PCR analysis revealed signs of a regenerative nature in bone marrow, which is manifested by a decrease in inflammation, adhesion and matrix formation, and an increase in anti-inflammatory and antioxidant effects comparable to GO'H transplantation [Lange K. , 2015].

In experiments conducted on F1(CBAxC57Bl/6) hybrid mice, the combined administration of quercetin (30-60 min. before γ-quantum irradiation of animals) and the immediate-acting radioprotector indralin (administration after irradiation) had a positive effect, at a non-lethal dose of 6.7 Gr post-irradiation recovery processes in hematopoietic tissues in the development of ONK after radiation, this was manifested in the acceleration of endogenous colony formation and the recovery of the spleen mass, in the low level of leukopenia on the 12th and 16th days from the moment of acute radiation injury [Vasin M.V., 2011].

In the bone marrow and blood of chickens, one of the factors was tried to observe the changes that occur under the influence of γ-rays. Dose- and time-courses of hematopoietic damage and recovery may not be the same for all animals, including poultry, as dose-response analysis of bone marrow death has revealed significant species differences. Characteristics of the effect of γ-irradiation on the cell composition of red bone marrow and peripheral blood of chicks at different ages [Vishnyakov A.I., Uvarova E.A., 2011].

In his experimental studies, Ivanov A.A. and all. [2013] mice after exposure to γ-rays at doses of 5.0 (LD20/30), 6.5 Gr (LD80/30), 7.0 and 10.0 (LD100/30) Gr (new method paper discs (Ø = 5 mm), which were moistened with a drop of urine and placed on Endo's solid nutrient medium) (CBAxC57Bl) studied the urinary microflora of F1. The method was tested in an endogenous infection model in mice infected with ORNA. An increase in bacteriuria was determined according to the dose of radiation exposure. Samara begins to manifest itself in the latent period of ONK, reaches its maximum expression during its peak, and normalizes during the recovery period. E. from the urine of irradiated animals. Coli, Proteus spp. and Enterococcus spp. separated.

The dynamics of wound surface healing according to the type of radiation wound and the applied cell product were studied in an experimental model of severe local radiation damage (SLD) after exposure to soft X-rays in rats. For this, 180-200 g. adult male Wistar rats were used. The study used a standard model of severe skin MNZs exposed to soft X-rays in a modified RAP100-10 apparatus. For the first time, the use of autologous cell products from adipose tissue was tested in an animal model of severe MNZ. It was found that the use of cells of the stromal-vascular fraction of adipose tissue for the treatment of early radiation injuries has a more pronounced therapeutic effect not only in the early period. All cell products have therapeutic effects in a model of long-term sequelae of radiation injury [2014].

The author [Safonova V.Yu., 2013] presented the results of studies on the effect of low-level ionizing radiation on the composition of IgG, IgM, IgA in the blood serum of animals. The change in their composition is shown under the influence of long-term and one-time irradiation at comparable doses. According to the author, the detected changes can serve as a prognostic test describing the negative effects of ionizing radiation. Irradiation of rats with a dose rate of 0.39 mGr/hour for 30, 60 and 90 days does not cause significant changes in the concentration of IgG, IgM, IgA. A single external radiation at doses of 0.5 to 0.8 Gr at a dose of 0.08 Gr/min causes a state of immunodeficiency in animals, as a result of which the concentration of IgG, IgM, IgA decreases on the 10th, 20th and 30th days after radiation exposure. occurs.

The effects of xenogenic cerebrospinal fluid (CSF) on white blood parameters of irradiated rats were investigated. Adverse effects of radiation on blood have been confirmed. A single injection of CSF at a dose of 10 ml/kg has no hemoprotective effect. Multiple administration of OMS at a dose of 2 ml/kg once every three days helps to normalize the number of leukocytes and restore the leukocyte formula, while restoring the functional activity of neutrophils. By the 30th day of the experiment, the number of leukocytes, the leukocyte formula and the indicators of cellular immunity approach those of the control animals. Our data justify the feasibility of using OMS and preparations based on it in radiation injuries [Kriventsov M.A., Devyatova N.V., 2017].

One of the directions in the search for long-term anti-radiation agents is preparations derived from animals and plants. According to the authors, the protective role of OMS has been proven under the adverse effects of external factors on the respiratory organs and the immune system. There is no clear opinion among the existing studies on the radioprotective effect of OMS on peripheral blood parameters and functional activity of protective cells. Administration of OMS to animals before irradiation has been proven to aggravate the transition to ANC, because the increased proliferation of hematopoietic cells as a result of the use of OMS

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led to the appearance of a large number of young, more radiosensitive cells [Kriventsov M.A., Devyatova N.V., 2017].

Comparison of the radioprotective effect of the soluble form of β-D-glucan obtained from the fungus Pleurotus ostreatus by oral administration at different doses in prophylactic/therapeutic regimens in experiments on white male mice. Comparison of the 30-day survival rate after total X-ray irradiation of rodents at doses of 7.5 and 8 Gr. evaluated through Post-irradiation administration of β-D-glucan (500 mg/kg intragastrically) at a dose of 7.5 Gr one hour after X-irradiation increased the 30-day survival of mice by 27% compared to the control group (47% and 20%, respectively). Therapeutic use of the drug at this dose in a prophylactic scheme 0.5 hours before irradiation or 2 hours after irradiation provided protection from death in 26% of mice irradiated with a dose of 8 Gr. The results show that β-D-glucan obtained from Pleurotus ostreatus has an anti-radiation potential when it enters the body of mice, has a positive effect on the survival of lethally irradiated animals, and has shown radiomitigator and radioprotective properties [Murzina E.V., 2020]. One of the directions in the search for long-term anti-radiation agents is preparations derived from animals and plants. According to the authors, the protective role of OMS has been proven under the adverse effects of external factors on the respiratory organs and the immune system. There is no clear opinion among the existing studies on the radioprotective effect of OMS on peripheral blood parameters and functional activity of protective cells. Administration of OMS to animals before irradiation has been proven to aggravate the transition to ANC, because the increased proliferation of hematopoietic cells as a result of the use of OMS led to the appearance of a large number of young, more radiosensitive cells [Kriventsov M.A., Devyatova N.V., 2017].

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The radioprotective effect of fucoidan isolated from the brown algae Fucus evanescens in the restoration of suppressed hematopoiesis was evaluated. It was found that sublethal administration of fucoidan to mice 1 hour after irradiation promotes faster recovery of hematopoiesis at the level of the spleen. On the 9th day after irradiation, a statistically significant increase in the number of endogenous colonies in the spleen and its mass was noted [Shutikova A.L., 2017].

To reduce mortality from radiation injury in laboratory animals after radiation, minced pieces of allogeneic thymus from prepubertal animals of the same species were transplanted into the anterior chamber of the eye through a 1.7±0.3 mm long corneal incision. The graft is placed directly on the iris of the eye as far as possible from the incision site. Transplantation was performed on the 3rd day after exposure to radiation. The method made it possible to reduce mortality from radiation exposure in experimental animals by determining the optimal effective volume of the injected graft and determining the optimal time for manipulation after radiation [Kulikov A.V., 2019].

A model of acute radiation bone marrow syndrome was developed in mice. In order to determine the course of the consequences of acute radiation damage, a medical-biological assessment of the effect of a single dose of γ-quantum on mice in the dose range of 3-9 Gr was carried out. From the 3rd to the 14th day (after radiation at a dose of 8 Gr - up to 25.5%), a dose-dependent increase in the expression of the cachexic effect compared to the background values was found in all exposed groups. The optimal doses of radiation for evaluating the hemostimulatory activity of radioprotective pharmacological agents are 5 Gr, 6.5 Gr for the analysis of survival and average life expectancy, and 8 Gr for studying the functional status of animals. The obtained results made it possible to justify the expediency of using a differentiated approach in choosing radiation doses and registration periods of radiobiological, physiological and hematological indicators in the screening of pharmacological activity of drugs for use at the stages of medical care in radiation injuries [Nikiforov A.S., 2017].

Tarasova N.B. and all. According to [2017], the amount of hemoglobin, erythrocytes, hematocrit and total protein in blood serum increased under the influence of single and triple administration of therapeutic and prophylactic immunoglobulin in irradiated animals, its bactericidal (1.2-1.3 times) and lysozyme (15% ga) activity, NFF, absorption ability of monocytes increased. Against the background of a decrease in T-suppressors, an increase in the number of T-helpers, an increase in the proliferation of V-lymphocytes was determined. After using the drug, the content of the main classes of immunoglobulins in blood serum increased.

Shashkarov V.P. and all. [2018] presented experimental data on the pathogenesis, course, and sequelae of moderate-severe OCN and combined radiation-heat injury in experiments on white rats exposed to external γ-irradiation at doses of 5.0 and 7.5 Gy and grade III-B thermal burns.

Experimental studies were carried out in Caucasian mice exposed to a single total irradiation with γ-quantum at doses of 5 and 6.5 Gr (dose rate 1.044 Gr/min). Hematopoietic growth factors (G-CSF at a dose of 0.2 mg/kg, erythropoietin at a dose of 0.03 mg/kg), somatotropin (at a dose of 0.3 mg/kg) and its releasing factors (hexarelin at a dose of 0.6 mg). /kg, ipamorelin at a dose of 0.6 mg/kg, CJC 1295 DAC at a dose of

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0.25 mg/kg, GHRP 6 at a dose of 1 mg/kg, GHRP2 at a dose of 1 mg/kg), as well as tissue protective peptides (ARA290 at 0.5 mg /kg dose). The anti-irradiation efficiency of trophic factors at a dose of 6.5 Gr was evaluated by analyzing the dynamics of 30-day survival, average life expectancy and body weight of animals; The dynamics of the main hematological indicators were analyzed under radiation at a dose of 5 Gr. It was found that the use of G-CSF after 6.5 Gr radiation increased the survival rate of irradiated animals to 29.0±10.0% compared to control (4.0±4.0%). Course administration of somatotropin CJC-1295 DAC and ARA290 slowed down the rate and depth of decrease in the number of platelets, helped to restore their level early in the post-radiation period from the 14th day [Sventitskaya A.M., 2017].

The antiradiation efficacy of a course of filgrastim treatment and the use of IL-1β in acute radiation injury bone marrow syndrome were investigated in a rat experiment. G-CSF therapy with the prophylactic use of IL-1b was found to be more effective than the use of these drugs separately, helps to increase survival, accelerates bone marrow myeloid growth and recovery of peripheral blood cells - leukocytes, neutrophils, lymphocytes [Salukhov V.V. et al., 2019].

The object of the study was to study the effectiveness of recombinant human thrombopoietin (riTPO) as a means of emergency pathogenetic treatment of ONK in experiments conducted in dogs. A single subcutaneous or intravenous injection of riTPO at a dose of 10 μg/kg 1.5–2 hours after irradiation was therapeutic in terms of both survival and blood counts. A particularly pronounced effect was noted in relation to thrombopoiesis, but also, to a lesser extent, in relation to granulopoiesis and lymphopoiesis. The results made it possible to consider the development of this cytokine as a means of emergency radiation therapy and a promising means of combating post-radiation thrombocytopenia [Rozhdestvensky L.M., 2013].

The object of the study was the blood of patients diagnosed with local radiation damage (NLD) and local radiation damage (LDL) taken 1-51 years after radiation injury. Mature mir34a, mir21, mir145, mir16, mir125b, let7a present in the total RNA fraction were reverse transcribed using special "stem-loop" primers. A significant decrease in mir34a, mir21 and an increase in mir145 in patients with MNZ were found in the blood of patients diagnosed with ONC. Analysis of individual microRNA values in the blood of patients with tumor disease, except for patients with basal cell carcinoma, showed that the changes correspond to the risk of developing carcinogenesis. The authors conclude that they have for the first time studied the functional activity of the p53-dependent system for maintaining genome stability in the blood of patients irradiated at clinically relevant doses after radiation injury. A decrease in mir34a, mir21 and an increase in mir145 in patients with MNZ were found in patients with ONK [Shulenina L.V. et al., 2014].

Exposure to ionizing radiation at a dose of 6 Gr causes a sharp violation of glutathione peroxidase activity in various parts of the brain of experimental animals, especially during the development of the NK (the 7th day after radiation). Under the influence of radiation, the most important changes are from glutathione peroxidase to hydrogen peroxide, the substrate of the enzyme is hydrogen peroxide, which is the final product of the superoxide dismutase reaction [Nagiev E.R., 2019].

Zvereva E.E. [2018] presented data on morphological changes in the pineal gland of experimental animals under the influence of ionizing radiation, which is of interest from the point of view of the organ's radiosensitivity and its participation in multilevel regulatory processes under conditions of injury. The bone marrow form of acute radiation sickness was modeled in an experiment on mature male Wistar rats exposed to ionizing gamma radiation. The structure of the organ was studied step by step for one month after exposure. Histological methods were used for gross staining of paraffin sections (with Van Gieson's hematoxylin and eosin) and semi-thin sections with toluidine blue. On the 3rd and 7th days, destructive events and clear swelling of all levels prevailed in the parenchyma of the gland, which was reflected by quantitative indicators of cell sizes and their structures. The injury was reversible only in some cells. Their death on the 14th day led to histotopographic restructuring of the organ, which was expressed in the form of smoothing of the boundaries between the superficial and deep zones, uneven distribution of cells with areas of stroma growth. Cellular content is monomorphic - light and dark pinealocytes and cells with intermediate nuclear, granular or powdery chromatin content of medium optical density, partial differentiation is lost. By the 30th day, this trend ended with a partial compensation of the injuries received. The author concluded that the pineal gland is a radiosensitive organ, and its stroma and parenchyma actively respond to ionizing radiation, compensating for damage. The cellular composition of pinealocytes and the dynamics of indicators of intracellular structure show significant damage, which is partially reversible.

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Dorojkina O.V. and all. [2015] investigated the effects of group and individual housing of outbred ICR (CD-1) male mice and inbred C57Bl6 mice on hematological parameters and immunity before and after proton irradiation. Group housing of intact animals resulted in a decrease in the number of karyocytes in the bone marrow and thymus mass. Irradiation of mice with 1 Gr of 171 MeV protons resulted in a reliable reduction of bone marrow cells when kept in groups compared to individuals. In individual maintenance of irradiated animals, there is a tendency to maintain a higher number of leukocytes in the peripheral blood and a higher proliferative activity of bone marrow cells, as well as a decrease in the level of aberrant mitoses compared to group maintenance. During the recovery period of radiation sickness, when the mice were kept in groups, the recovery process continued at a rapid pace.

The author [Sarukhanov V.Ya., 2016] in his study considered the numerical parameters of the death of dogs weighing 10-12 kg according to the dose and dose strength of external radiation. Comparison of LD50 values for adult sheep, pigs, dogs, donkeys and mice at a fixed dose of 4 Gr/h showed that the ruminants most sensitive to external exposure were sheep, followed by dogs, donkeys and pigs, followed by rodents - mice.

In experimental animals exposed to the dust-radiation factor for a long time, changes manifested by a decrease in the number of leukocytes, the number of SD3+, SD4+, SD8+, TsIK and immunoglobulins of different groups, as well as a decrease in NFF, were revealed. The dose-dependent formation of immunosuppression is characterized by T-lymphopenia with predominant SD4+ cells and phagocytosis activity, a decrease in the functional activity of natural killers (NK-cells), a decrease in their number, damage to the main function of the immune system, i.e. control of the genetic stability of the cell composition with the embodiment of carcinogenic effects.

The success of treatment for ANC depends on immediate supportive care. In patients with limited hematopoietic potential, hematopoietic stem cell (HSC) transplantation remains the only option. Mesenchymal stem cell (MSC) therapy may be an alternative for radiation-damaged patients. In vitro experiments on the differentiation of human MOH (iMOH) into GO'H genetic cells and endothelium have shown that MOHs change the morphology and gene expression profile and possibly have hematopoietic potential. Mouse MO'H (sMO'H) were obtained from bone marrow, tagged with eGFP, and cloned. Targeted MO'H was administered intravenously to lethally irradiated mice. Long-term survival of recipients with restoration of hematopoiesis after transplantation of MOH alone without the addition of GO'H was found. Quantitative PCR analysis of chimerism detected target cells in the peripheral blood immediately after injection and in the lung 24 hours later. But in late stages, no donor cells were found in any of the tissues studied. Despite the rapid loss of donor cells, microarray and PCR analyzes revealed signs of a regenerative nature in the bone marrow, which was manifested by a decrease in inflammation, adhesion and matrix formation, and an increase in anti-inflammatory and antioxidant effects comparable to GO'H transplantation. Administration of secreted MOH-microvesicles has been shown to have the same protective effect as administration of cells. MOCs protect endogenous hematopoiesis by secreting trophic factors and modulating the activity of MOC spaces, and found that radiation-induced hematopoiesis can be a rapid and effective first aid in failure [Lange K., 2015].

Thus, due to the fact that there have been few studies on the morphological changes caused by radiation, the scientific sources are also insufficient. However, there are still few accurate data, so it is appropriate to continue research on this topic.

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