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POSSIBLE EFFECTS OF THE EXPOSURE TO IONIZING RADIATION ON THE PATIENTS RECOVERED FROM COVID-19

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The aim. *To conduct an analytical literature review on the possible impact of SARS-CoV-2 on the radiosensitivity of the human body and justify the relevance of radiobiological research in this area.*
Materials and methods. *Analysis of data from biological dosimetry / indication of radiation lesions of human peripheral blood T-lymphocyte chromosomes under medical irradiation for comparison with radiosensitivity in the patients recovered from COVID-19 (Scopus International Scientific Metric Database, IAEA guidelines, 2011).*
Results. *With the ongoing COVID-19 pandemic, forecasting and clarifying of the mechanisms of distant effects resulting from interactions between ionizing radiation and the SARS-CoV-2 virus play an important role. The difficulty in solving this problem is caused by the fact that the global science has no exhaustive information on the possible influence of this virus on radiation-induced effects. The attention of the professional community is drawn to the possible impact of SARS-CoV-2 on the radiosensitivity of the body of patients recovered from COVID-19 and a hypothesis is first proposed regarding the mechanism on how to increase it based on the development of systemic long-term inflammation. Therefore, clinical trials of low-dose radiotherapy for the treatment of COVID-19-related pneumonia involve preliminary radiobiological studies to answer the following question: does the SARS-CoV-2 virus affect the radiosensitivity of the human body? Long-term experience of the author of this paper in biodosimetric (cytogenetic) studies allows her to recommend the peripheral blood lymphocyte test system with chromosome aberration's analysis as the most radiosensitive cell model.*
Conclusions. *Clinical trials of low-dose radiotherapy for the treatment of COVID-19 pneumonia involve a preliminary radiobiological study to answer the following question: does the SARS-CoV-2 virus affect the radiosensitivity of the human body? The most optimal approach for the solution of this problem is the use of test-system of human peripheral blood lymphocytes' culture with the subsequent cytogenetic analysis. It will allow investigating changes in the "dose-effect" "cell cycle stage-effect" dependencies, as well as changes in individual radiosensitivity under the influence of SARS-CoV-2 virus*
Keywords: *COVID-19, ionizing radiation, low-doses, long-term effects, cytokine "storm", lymphocytes, radiosensitivity, low-dose radiotherapy, computed tomography, radiobiological studies*

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1. Introduction

The ongoing pandemic of COVID-19 coronavirus infection has resulted in more than 70 million cases worldwide and more than 11.6 million deaths as of December 2020 [1]. In Ukraine, the first case of COVID-19 was reported in Chernivtsi on 29 February 2020. The most common clinical manifestation of new coronavirus infection is atypical bilateral pneumonia. SARS-CoV-2 infection impairs water-salt metabolism and protein transport by fusing cells and affecting cell membrane permeability. Under these conditions, surfactant deficiency develops, leading to the alveolar collapse and pulmonary distress syndrome [2]. In general, there is limited information on the epidemiological and clinical features, methodology of diagnosis and treatment of this disease [3, 4]. Since December 2019, the treatment of the disease has been chosen empirically, although its pathogenetic aspect is somewhat better developed [5, 6]. To date, tests are used to detect the causative agent COVID-19, but the virus is detected in only 30–60 % of infections by collection of material (oropharyngeal and nasal swabs) [7]. The long-term effects on patients recovered from SARS-CoV-2 infection are not yet known, and the likelihood and severity of disease during reinfection remain uncertain [4].

The aim. To conduct an analytical literature review on the possible impact of SARS-CoV-2 on the radiosensitivity of the human body and justify the relevance of radiobiological research in this area.

2. Materials and methods

Analysis of data from biological dosimetry/indication of radiation lesions of human peripheral blood T-lymphocyte chromosomes under medical irradiation for comparison with radiosensitivity in the patients recovered from COVID-19 (Scopus International Scientific Metric Database, IAEA guidelines, 2011).

3. Results

The SARS-CoV-2 virus has been the focus of researchers worldwide. In 2020, it was established that the SARS-CoV-2 viral particle is represented by 4 types of structural proteins, among which the S-protein (spike) plays a major role in virus penetration into the host cell [8]. At the same time [9] it was shown that this virus mutates slower than other human RNA viruses as it contains the gene responsible for correcting the replication of DNA molecules. The most dangerous property of this virus is its ability to create an overactive innate immune system through damage to macrophages and induction of a cytokine “storm”, which causes severe pathogenetic complications [10]. At the same time, intense discussions are beginning about the use of radiation technology to reduce the potential risk of developing and treating pneumonia in patients with COVID-19 [11, 12]. Some researchers believe that the cytokine “storm” caused by interleukin-6 (IL-6) in COVID-19 pneumonia resembles rheumatic arthritis, which is successfully treated with low-dose radiotherapy (LDRT). At the same time, a decrease in the number of CD4+ T- and CD8+ T-cells in the peripheral blood of COVID-19 patients is observed under the influence of radiation [12]. It is believed that the greatest therapeutic effect is achieved by irradiation in the dose range of 0.3-0.7 Gy, while increasing the dose, on the contrary, may intensify the inflammatory process [13–15]. Other researchers believe that lungs affected by SARS-CoV-2 cannot serve as a local target for irradiation and only general LDRT of COVID-19 patients can be effective [11]. However, even this scenario of radiation treatment of COVID-19 patients presents several limitations: the occurrence of radiation-induced genomic instability; negative interaction between ionizing radiation and COVID-19 infection, given the different pathogenesis of viral and bacterial pneumonia [16].

Due to the widespread use of chest computed tomography (CT) for the diagnosis of COVID-19, studies assessing radiation exposure and radiation risks, including those related to the development of cancer pathology, are of particular relevance. A number of studies on the carcinogenic effects of low doses of ionizing radiation (IR) have been performed previously. At present, there are still differences in the definition of low-dose radiation. Close attention to small doses is explained, first, by the well-known basic radiobiological paradox – disproportionately high biological effect in comparison with the absorbed energy. The dose is a macroscopic value that characterizes the average energy absorbed per unit mass of irradiated substance. That is, it is the dose at which one sensitive cell volume has an average of one ionizing track. According to the recommendations of the UN Scientific Committee on the Effects of Atomic Radiation, small doses have higher values than those due to the natural level of radiation, i.e. 1–40 cGy. Doses not exceeding 40–50 cGy are considered to be small doses for the most radiosensitive cells of the human body – blood lymphocytes.

In this context, we have for the first time determined the linear nature of the dose dependence of malignant neoplasms in a survey of 17,000 liquidators of the Chernobyl disaster using the method of biological (cytogenetic) dosimetry, as well as models of mathematical statistics – linear, linear-quadratic and spline regression. Because of a large-scale and long-term radiation-epidemiological study and taking into account the paradigms of radiobiology, the carcinogenic danger of exposure to radiation in small doses on the body of liquidators regardless of their age was established [17, 18].

In [19], based on a linear threshold-free model, it was shown that medical irradiation of the French population causes 14.3 % of cancers of radiation origin. The authors of [20] also confirm that stochastic (carcinogenic) effects could be caused by radiation in small doses.

Commenting on the doses of pulmonary radiation used in clinical practice for the diagnosis and treatment of patients recovered from COVID-19, the authors of the study [21] argue that a dose of no more than 0.5 Gy provides an acceptable level of lifelong radiation risk (no more than 1 %). In [22], it was found that the radiation risk for single, double, and triple CT of the chest for patients regardless of their age is low. It is concluded that the usage of modern computed tomography, which allows the use of low-dose algorithms for computer diagnostics, will significantly reduce the radiation exposure of patients [23].

The above-mentioned data suggest that the COVID-19 pandemic may make significant adjustments to the formation (increase) of radiosensitivity of those patients who have suffered from this disease. It should be considered that the increased systemic-inflammatory activity caused by the SARS-CoV-2 virus persists for a long time after recovery [24].

We recently proposed a hypothesis [25] that the evolution of radiosensitivity in patients recovered from COVID-19 exposed to low-dose radiation, including for medical purposes, may progress by activating sequential mechanisms: increased systemic inflammation → increased cell oxygenation → increased radioactivity background of lymphocytopenia → increased risk of radiogenic carcinogenesis.

In order to confirm or exclude the proposed hypothesis, it is necessary to solve a number of questions involving the paradigms of radiobiology. The effect of ionizing radiation on immunity is evident in the early and distant period after exposure. The lymphoid tissue is the most radiosensitive in the human organism. The death of individual subpopulations of lymphocytes is possible already under irradiation in the low dose range. A decrease in the content and proliferative activity of T-lymphocytes and their migratory properties was detected early after exposure [26]. However, it should be considered that T-lymphocytes play the most important role in the immune response to viral infection. This explains the need for further investigation of the mechanisms of the primary processes underlying the development of the inflammatory response to radiation damage of T-lymphocytes in patients recovered from COVID-19. These processes are superimposed on endogenous cytokine responses, which cause prolonged inflammatory responses to SARS-CoV-2 virus [24]. It is suggested that increased systemic inflammatory activity, which persists for a long time in the patients recovered from COVID-19, in combination with low-dose range irradiation (in repeated diagnostic radiation procedures, in particular computed tomography) and high-dose range irradiation (radiation therapy of cancer patients) could significantly modify (increase) radiosensitivity of cells, tissues. This may cause the development of associated diseases of the blood circulatory system, nervous system, and others. The potential risks of the clinical use of LDRT for the treatment of COVID-19, according to many authors, exceed the potential benefits. This means that the anti-inflammatory effects of LDRT may not be effective against SARS-CoV-2. Therefore, in our opinion, clinical trials of LDRT should be preceded by radiobiological studies using cellular models (e.g., T-lymphocytes) highly sensitive to irradiation in a wide range of doses. Use of test-system of human peripheral blood lymphocytes culture with further analysis of frequency and spectrum of spontaneous and radiation-induced chromosome aberrations, evaluation of individual radiosensitivity based on G_2 chromosome test will allow estimating the change of “dose-effect” and “cell cycle stage-effect” dependencies under the influence of SARS-CoV-2 virus.

4. Conclusions

Clinical trials of low-dose radiotherapy for the treatment of COVID-19 pneumonia involve a preliminary radiobiological study to answer the following question: does the SARS-CoV-2 virus affect the radiosensitivity of the human body? The most optimal approach for the solution of this problem is the use of test-system of human peripheral blood lymphocytes’ culture with the subsequent cytogenetic analysis. It will allow investigating changes in the “dose-effect” “cell cycle stage-effect” dependencies, as well as changes in individual radiosensitivity under the influence of SARS-CoV-2 virus.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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