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POINT OF VIEW

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LONG-TERM EXPOSURE TO LOW DOSES OF IONIZING RADIATION AND COVID-19 PANDEMIC: ONCOHEMATOLOGICAL ASPECTS

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For more than 35 years after Chornobyl catastrophe, about 5 million people in Ukraine, Republic of Belarus and Russian Federation inhabit the territories that are residually contaminated with long-lived radionuclides such as ^{137}Cs, ^{90}Sr. The previous studies of the Reference Laboratory operating at RE Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology allowed specifying the effects of the protracted low dose irradiation on the state of the hematopoietic and lymphoid tissues resulting in the increased proportion of the B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma and acute myeloid leukemia among the patients referred from the contaminated areas of Ukraine. Since the beginning of 2020, these effects of radiation were superimposed by the factors associated with COVID-19 pandemic. SARS-CoV-2 infection is associated with the significant impact on hematopoiesis and immune system. Particular attention should be given to the role of such combined burden in the development of the immunodeficiency-associated lymphoid neoplasms. The extensive studies of the combined effects of low dose irradiation and COVID-19 within the large affected populations could be made a priority in future endeavors of epidemiologists and oncohematologists.
***Key Words*: ionizing radiation, COVID-19, neoplasms of hematopoietic and lymphoid tissues.**

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INTRODUCTION

The vast epidemiological studies provided the broad evidence of the association between the exposure to ionizing radiation and the increased risk of the stochastic (leukemogenic and carcinogenic) consequences. The predominant information about such consequences has come from studies of the cohort of Japanese A-bomb survivors who have now been followed for more than 60 years. The Chornobyl catastrophe of 1986 becoming one of the worst radiation disasters in the history of the nuclear industry spotlighted the problems of the oncological consequences of the protracted exposure of the numerous populations to low dose radiation. In Ukraine, Republic of Belarus and Russian Federation more than 5 million people inhabit the territories that are residually contaminated with long-lived radionuclides such as ^{137}Cs, ^{90}Sr and transuranic elements. The population of the most contaminated areas in Kyiv, Zhytomyr, Rivne, Chernihiv, and Cherkasy regions amounts to more than 2.6 million. About 100 thousand residents of the districts assigned as the areas of strict control still receive more than 1 mSv annually. The estimated average effective doses accumulated for 30 years after Chornobyl catastrophe for the general population of the most contaminated areas are in the range of 10–50 mSv [1]. Nevertheless, the assessment of the stochastic effects of ionizing radiation in population of the contaminated areas of Ukraine faces with the difficulties because of the uncertainty in the estimation of the actual individual doses.

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Abbreviations used: AML – acute myeloid leukemia; CLL – chronic lymphocytic leukemia.

HEMATOLOGICAL MALIGNANCIES IN UKRAINE IN POST-CHERNOBYL PERIOD

In Ukraine as well as in Russian Federation and Republic of Belarus, analytical epidemiologic studies for evaluating the possible risk of leukemia in persons permanently exposed to low-dose radiation (mostly internal exposure) have not been initiated except for a few limited analyses of the incidence trends and studies covering small territories [2, 3]. As a result, the post-Chornobyl data on the hematological malignancies in Ukrainian population residing in the areas with different levels of the contamination with radionuclides are incomplete and inconsistent. There are some reasons underlying the difficulties in assessment of real patterns of hematological malignancies in Ukraine in post-Chornobyl decades. Among them, the insufficient quality of diagnosis and the undercounting of several nosologic forms of leukemia outlines in the modern classifications of the malignant diseases of hematopoietic and lymphoid tissues. Moreover, the Bulletin of National Cancer Registry of Ukraine combines several different forms of leukemia into aggregated categories that does not allow analyzing the probable association of intrinsically different forms and cytological variants of hematological malignancies with radiation exposure.

Nevertheless, the statistical data extracted from the National Cancer Registry of Ukraine may be useful for the crude assessment of some over time trends in the incidence of leukemia as an aggregated group both in Ukraine as a whole and in different regions of the country. Since 1976, the annual incidence of hematological malignancies in total (C81–C96 according to ICD-10) tended to increase both in the regions of Ukraine referred to as contaminated with radionuclides or conventionally non-contaminated suggesting that not only radiogenic factors contribute to this increasing trend. Currently, the incidence of hematological malignancies amounted to 19.3 per 100,000 of population in contaminated regions and 15.5 per 100,000 in non-contaminated regions.

There are several in-house sources of information in Ukraine that provide the exact diagnoses of oncohematological diseases in complying with the requirements of the current classifications although such diagnostic activity does not cover the entire population of Ukraine. In particular, the database of the Reference Laboratory of R.E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology of the National Academy of Sciences of Ukraine amounted to about 30 thousand cases of the hematologic malignancies diagnosed in 1996–2017 among the patients from more than 20 regions of Ukraine [4]. The precise diagnosis of the various forms of malignant tumors of hematopoietic and lymphoid tissues was provided using the techniques of cytomorphology, cytochemistry and immunocytochemistry.

According to the currently accepted opinion shared by many epidemiologists, increased leukemia risk as a consequence of protracted radiation exposure could not been revealed due to the lack of the statistical power [5, 6]. Nevertheless, in our opinion, some approaches could be helpful for understanding the long-term oncohematological consequences of Chornobyl disaster in Ukraine. While in-house analysis could not provide the data on leukemia incidence, it would be useful for studying the year-by-year dynamics in relative contribution of certain forms of leukemia in different regions of Ukraine with different levels of radionuclide contamination hinting at the possible association between radiation exposure and some specific forms of hematological malignancies.

According to our data and the data presented in the issues of “Indicators of Hematological Service Activity in Ukraine”, the average (2010–2017) number of chronic lymphocytic leukemia (CLL), multiple myeloma and acute myeloid leukemia (AML) patients per 100,000 of population in contaminated regions of Ukraine was higher compared to that in relatively clear regions while the differences expressed by patients per 100,000 of population in contaminated and relatively clean regions for chronic myeloid leukemia and myelodysplastic syndromes have not been revealed. The slight shift in the proportion of AML and CLL in the total diagnosed cases of all hematological malignancies from contaminated areas has been evident. Therefore, several differences in the relative distribution of specific forms of oncohemathological pathologies among the patients from contaminated and non-contaminated regions of Ukraine in post-Chernobyl period have been revealed. Of particular concern is the demonstrated association between CLL and radiation, since initially no CLL excess was evident among A-bomb survivors in Japan. However, some pieces of recent evidence strongly suggest the association between long-term exposure to ionizing radiation and CLL risk [7, 8].

Therefore, we have managed to demonstrate a steady trend in post-Chernobyl redistribution of the specific forms of hematological malignancies in the regions of Ukraine suffered from the contamination with radionuclides although the design of our study did not provide the stringent epidemiological indices such as leukemia incidence and mortality. Nevertheless, our database could be useful for further descriptive and analytical epidemiological studies on the association of the protracted low dose irradiation and several specified forms of hematological malignancies.

CANCER-RELATED ASPECTS OF COVID-19 EPIDEMIC: BACKGROUND AND ASSUMPTIONS

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) that causes coronavirus disease COVID-19 initiated a global health crisis. Since WHO declared a pandemic in March 2020, nearly 175 million people caught the disease that became a cause of about 3.7 million deaths.

In our opinion, it seems reasonable to study whether this pandemic may be a trigger for the development of oncohematological diseases and whether some excess of these diseases may be predictable. These probable sequelae concern not only the cohorts of patients recovering from severe forms of COVID-19 but also those who had mild and moderate disease [9].

There are some seemingly common features shared in pathogenesis and some clinical peculiarities of SARS-CoV-2 infection and radiation injuries, in particular, multisystem failure destroying the biological homeostasis [10]. COVID-19 is associated with hematological and immunological abnormalities [11].

Lymphopenia. Low lymphocyte count is one of the common clinical indicators predicting the severity of the disease course in COVID-19 patients [12]. The mechanisms underlying lymphopenia in COVID-19 and some other viral infections are not completely understood [12, 13]. A number of possible reasons had been put forward such as direct invasion of lymphocytes, hyperlactic acidemia and suppression of lymphoid cell proliferation, and inflammatory cytokine storm resulting in apoptosis of lymphocytes [14]. In COVID-19 patients, the absolute count of T and NK cells in peripheral blood is depleted [15]. In severe cases, a significant decrease in lymphocyte subpopulations, especially $CD4^+$ and $CD8^+$ T cells is even more pronounced [15, 16]. Meanwhile, T cells are negative for ACE-2 receptors representing the entry point of virus in different types of human cells. CD147 also known as Basigin or EMMPRIN has been recently proposed as an alternative route for SARS-CoV-2 penetration into the cells [17]. This molecule was originally identified as a T cell activation-associated antigen. The transmembrane glycoprotein CD147 is highly expressed by the activated T cells. Some data disclose the role of CD147 in pathogenesis of several hematological malignancies [9, 17]. CD147 expression is also detected on neoplastic cells in several cancers. Today, several new data on the molecular basis of the interaction between SARS-CoV-2 spike protein and CD147 in COVID-19-associated lymphopenia have been presented. SARS-CoV-2 induced NKG2 expression that correlates with the exhaustion of CD8+ T cells and NK cells [18]. In addition, T cell depletion is accompanied with decreasing B cell count with concomitant detection of plasmacytoid lymphocytes in blood [19].

Thrombocytopenia. Several data suggest that lower platelet count ($< 150 \times 10^9$/L) is associated with severity of the COVID-19 course and its progression [20, 21]. The mechanisms of COVID-19-associated thrombocytopenia are under study. Among them are direct action of virus on hematopoietic stem cells and progenitor cells of bone marrow, increased platelet destruction by autoantibodies, and platelet aggregation in the lung [22]. Cytokine storm with elevation of several interleukins may also lead to thrombocytopenia and hemophagocytic lymphohistiocytosis [23].

Anemia. In contrast to lymphopenia and thrombocytopenia, autoimmune hemolytic anemia does not represent the major problem in COVID-19 patients [12]. Nevertheless, we believe that the possible effects of SARS-CoV-2 on early erythroid progenitor cells deserve an in-depth analysis.

FUTURE OUTLOOK

The problem of the combination of coronivirus effects and long-term exposure to the low doses of ionizing radiation, both factors affecting hematopoietic system, seems to be of particular attention while many variables mediating such effects still remain mostly conjectural. Nevertheless, this problem may well become of high priority in the forthcoming years taking into account that both COVID-19 pandemic and mass-scale vaccination kick into high gear. The in-depth study of the pathogenesis and clinical course of COVID-19 in the patients from the regions with the residual contamination with radionuclides after Chernobyl accident is required. The data pertaining to COVID-19 might be compared with the data on the patterns of the tumors of hematopoietic and lymphoid tissues in the patients from the same regions. Such comparative data may be of high concern for the contaminated regions of both Ukraine and Russian Federation and Republic of Belarus.

Taking into account the impairments in hematopoiesis and both innate and adaptive immunity in COVID-19 patients [9, 24], one may suggest the primary impact on the immunodeficiency-associated lymphoid neoplasms. No less important are the problems underlying the mass-scale vaccination at the height of pandemics in the setting of the protracted low dose irradiation. This concerns not only the generation of the stable immunity against coronavirus but also the possible impact (positive or negative) on the development of the various forms of the lymphoproliferative disorders.

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ТРИВАЛА ДІЯ ІОНІЗУВАЛЬНОГО ВИПРОМІНЮВАННЯ В НИЗЬКИХ ДОЗАХ ТА ПАНДЕМІЯ COVID-19: ОНКОГЕМАТОЛОГІЧНІ АСПЕКТИ

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Упродовж більш ніж 35 років після чорнобильської катастрофи близько 5 млн людей в Україні, Республіці Білорусь та Російській Федерації мешкають на територіях із залишковим забрудненням триваложивучими радіонуклідами, такими як ^{137}Cs, ^{90}Sr. Попередні дослідження Референтної лабораторії на базі Інституту експериментальної патології, онкології і радіобіології ім. Р.Є. Кавецького дозволили визначити вплив тривалої дії низьких доз іонізувального випромінювання на стан кровотворної та лімфоїдної тканин, було зафіксовано збільшення частки випадків В-клітинної хронічної лімфоцитарної лейкемії та гострої мієлоїдної лейкемії серед онкогематологічних хворих із забруднених радіонуклідами територій України. З початку 2020 р. на ефекти, спричинювані випромінюванням, накладаються фактори, асоційовані з пандемією COVID-19. Інфекція SARS-CoV-2 асоціюється із значним впливом на кровотворну та імунну системи. Особливу увагу слід приділити можливій ролі такого сукупного навантаження в розвитку лімфоїдних новоутворень, асоційованих з імунодефіцитами. Поглиблене вивчення ефектів тривалого опромінення в низьких дозах в поєднанні з факторами, обумовленими COVID-19, у зазначених популяціях, які зазнають такого впливу, може стати одним з пріоритетних напрямів досліджень епідеміологів та онкогематологів.

Ключові слова: іонізувальне випромінювання, COVID-19, новоутворення кровотворної та лімфоїдної тканин.