REASONS FOR THE UNDERTAKING RESEARCH SUBJECT AND AIM OF THE PROJECT: The coronavirus disease 2019 pandemic (COVID-19) made the whole world aware of the importance of the proper functioning of the immune system, especially in elderly persons and suffering from chronic diseases. Recurrent infections constitute a significant clinical problem in patients with chronic lymphocytic leukemia (CLL), being the most common cause of mortality in this group of patients. CLL patients experience symptoms of respiratory tract infections particularly often. One of the most common causes of infections nowadays is SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2). The clinical observation of the author of the project showed that a significant percentage of patients with CLL is not able to eliminate SARS-CoV-2 for longer period of time comparing to healthy persons (even over 4 months) and experience symptoms of infections not only longer than people in the general population, but also a history of infection may lead to the development of many organ complications or - in the long term - possibly also faster progression of CLL. Regardless of the current pandemic, the highly oncogenic Epstein-Barr virus (EBV) has remained a significant problem in people with impaired immune function, infecting more than 90% of the world population and - following primary infection - EBV stays lifelong in its latent form. In patients with impaired functioning of the immune system, especially interferonopathies, the virus reactivates and can lead to many disorders, including the development of cancers. Long-term antigenic stimulation, induced by EBV reactivation and/or other chronic/recurrent infections, may lead to the development of specific response "anergy" and the development of an "immune risk profile", often observed in the elderly, including those with CLL. The aim of the presented project is to assess the course of SARS-CoV-2 infection in patients with CLL depending on the indicators of immune disorders and reactivation of EBV infection, with particular emphasis on the role of interferons as natural compounds with therapeutic potential. Initial observations of the author of this project showed that patients with CLL who developed severe, including fatal complications from SARS-CoV-2 infection, lacked the ability to produce interferon alpha and gamma, and showed signs of chronic reactivation of EBV infection. In the light of our own observations, reports of other authors, as well as the case report of an effective treatment with alpha interferon (also using the nebulization method) in a patient diagnosed with chronic active EBV infection, published by our team, a detailed evaluation of the role that interferon therapy can play in the treatment of viral infections in patients with interferonopathies seems justified.

RESEARCH DESCRIPTION: The project will be carried out in *ex vivo* (CLL patients and healthy controls), as well as *in vitro* and *in vivo* conditions in the zebrafish animal model. The study group will consist of 200 patients with CLL (100 patients characterized by reactivation of EBV infection and 100 patients without signs of EBV reactivation), who are in the clinical period that do not require the implementation of CLL treatment yet. The control group will consist of 100 healthy persons, matched in terms of sex and age to patients with CLL. We assume a 3-year observation period for the above groups. The research will use molecular biology methods-expression of genes encoding innate response receptors, interferons and molecules that indicate cellular anergy. At the same time, the tested molecules will be assessed by multicolor flow cytometry. We will compare the humoral and cellular responses in people who have had SARS-CoV-2 infection and those who have been or will be vaccinated against COVID-19.

THE MOST IMPORTANT EXPECTED EFFECTS: Detailed analysis of the relationship between the clinical course of SARS-CoV-2 infection and selected parameters of the immune response in CLL patients will allow to distinguish a group of patients with interferonopathies, particularly predisposing to severe viral infections. Assessment of the durability of the cellular (memory cells) and humoral response after SARS-CoV-2 infection in relation to the duration of the indicators of an adequate immune response to the anti-SARS-CoV-2 protective vaccinations will allow to assess the effectiveness of vaccines in CLL patients. The zebrafish animal model with implanted CLL cells will serve as a reflection of the processes taking place in the human body during CLL, influenced by the administration of interferons, depending on the presence of EBV reactivation markers and SARS-CoV-2 co-infection. Preliminary studies suggest that the heterogeneous course of CLL is associated not only with recognized prognostic factors, but also with defects in the immune system, including decreased secretion of interferons in response to infections, mainly manifested by EBV reactivation. If the results confirm the role of co-infection with SARS-CoV-2 and EBV reactivation in the progression of CLL, this could open up new research directions and contribute to the development of effective immunomodulation strategies in CLL. We hope that the implementation of the project will allow for the development of important premises for the establishment of a diagnostic procedure that will select CLL patients at particular risk of the most serious complications of SARS-CoV-2 infection, optimize the vaccination strategy and ensure effective stimulation of the immune system using interferons.