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Review Article

Risk of coronavirus disease 2019 (COVID-19) infection on leukemia patients: basic science to clinical aspect

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ABSTRACT

In March 2020, the Coronavirus disease 2019 (COVID-19) pandemic was announced by the World Health Organization (WHO). A novel strain of coronavirus, recently named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) created the disease, which showed symptoms similar to SARS. The virus's bond determines its pathogenesis with its host's cell receptors, mainly the Angiotensin-Converting Enzyme 2 (ACE2). It is a factor of the Renin-Angiotensin System (RAS), that holds a vital function in hematopoiesis of hematologic malignancies. There is mRNA expression of the RAS component, so there is an increase in ACE2 levels in patients with leukemia, primarily the myeloid type. Acute Myeloid Leukemia (AML) malignant blood cells can escape from the immune system through a biochemical mechanism that causes AML cells to deactivate Natural Killer (NK) and cytotoxic lymphoid cells (cytotoxic T cells (CTC). This review article aims to explain the molecular mechanism, including leukemia patients' immune system with COVID-19 and recommendations for patients and hemato-oncologists.

Keywords: ACE2, COVID-19, Immune system, Leukemia, SARS-CoV

Introduction

The coronavirus pandemic has become a universal well-being matter. The virus spread all over the world and still has not stopped, after reporting the first case in Wuhan, China, in December 2019. The most recent data recorded that the virus has spread and contaminated above 700 thousand people and has caused the death of above 36 thousand patients worldwide [1-4]. Previous research stated that the virus had been found in Chinese horseshoe bats. A wet market in Wuhan where wild animals were sold as food or pets has been suspected to be the epicenter of this outbreak [5].

The etiology of COVID-19 is transmitted through droplets or small particles coming out of a sick person's mouth (saliva) containing the virus [6]. The cases reported in Italy confirmed that patients who die are in their 80s, while in China, it is the patients in their 60s. It means the older a person, the more contributing diseases they have, the worse their conditions would be if the virus infected them. In the elderly, there is a decrease in T cell and B cell production in the bone marrow and thymus. There is also a decrease in mature lymphoid function in secondary lymphoid tissues. These cause the immune response in the elderly not to be as strong as that of a young person [7]. Besides that, other conditions that cause people to have a higher risk of death when infected with coronavirus are comorbidities such as chronic respiratory diseases, diabetes mellitus, coronary artery disease, hypertension, and cancer included hematologic malignancy, especially leukemia [8]. This review will discuss the pathophysiology of leukemia and its correlation with the SARS-CoV-2 infection susceptibility. Additionally, the study will

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enlighten the hemato-oncologist to protect their patients in the recommendation part.

Epidemiology of COVID-19 and leukemia

Currently, in China, where the first case of COVID-19 was found, 82.545 positive cases and 3.314 deaths due to COVID-19 have been recorded [2]. The first case in China was reported in Wuhan, Hubei Province, and then cases kept appearing in other provinces around Hubei [7, 9].

All over the world, 198 countries have reported positive cases of COVID-19 and 158 countries with local transmission. WHO's most recent report stated 750.890 confirmed cases and 36.405 deaths from COVID-19 [2]. The country with the most confirmed cases in the United States of America, with 161.199 verified cases and 2.850 deaths [3]. In March 2020, due to a high number of confirmed cases and deaths worldwide, the World Health Organization announced COVID-19 as a pandemic [1].

Leukemia is a malignancy that is commonly found in children and adults. The four major subtypes of leukemia most widely found are acute lymphoblastic leukemia (more common in children), chronic myelogenous leukemia, chronic lymphocytic leukemia, and acute myelogenous leukemia [10]. Leukemia causes more deaths in men (cumulative risk 0,40%) than women (cumulative risk 0,26%) [11].

The GLOBOCAN report in 2018 stated there were 437.033 new cases of leukemia globally and caused 309.066 deaths. According to the observational data, leukemia as the 13th malignancy with the most significant number of new cases and the tenth-largest malignancy cause of death in 2018 [11].

Virology of SARS-CoV

COVID-19 is a respiratory disease resulted by the novel coronavirus [12]. Its beta coronavirus has an envelope including a positive single-stranded RNA genome (26-32 kb) **(Figure 1)** [13-15]. The International Committee on Taxonomy of Viruses (ICTV) announced this new coronavirus had been named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) on February 2020 [13, 14]. Human coronaviruses belong to the alpha (HCoV-229E and NL63) and beta (HCoV-HKU1, SARS-CoV, MERS-CoV, and HCoV-OC43) coronavirus genera [16, 17]. B-CoV was found in all pneumonia patients admitted from 18 to December 29, 2019, in China. The 88% of isolated b-CoV showed identities of viruses from bats, the Severe Acute Respiratory Syndromes (SARS)-like coronaviruses, and approximately 50% were MERSCoV [18].

Coronavirus is a zoonotic pathogen with a high mutation level and is a pleomorphic RNA virus with a crown-like peplomer sized 80-160 nM [19-21]. The SARS-CoV-2 genome is like CoV, with 10 open reading frames (ORFs). The first two-thirds of ORFs (ORF1a/b) encodes virus polymerase (RdRp), an RNA synthesis material, and two non-structural polypeptides which are not involved in host modulation response (ORF1a-ORF1b) [22]. Another one-third of SARS-CoV-2's ORFs encodes 4 structural proteins, nucleocapsid protein (N), the spike protein (S), membrane protein (M), an envelope protein (E), and several additional proteins that function in virus replication are still unknown. The Angiotensin-Converting Enzyme 2 (ACE2) is needed as a receptor to fuse the SARS-CoV-2 and its host cell **(Figure 2)**. The bond between virus and host cell receptors determines the pathogenesis of infection [23-26].

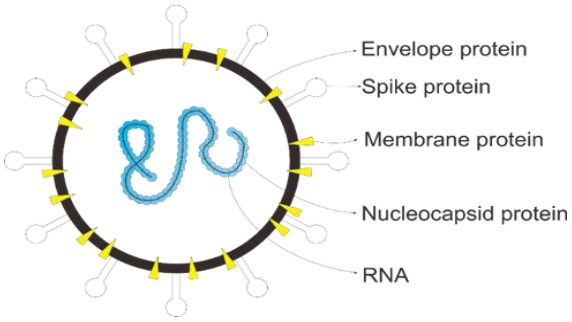

Figure 1. SARS-CoV-2 Structure. (Taken with Modifications from Peiris *et al.*, 2003) [26]

Pathophysiology of myeloid leukemia

Acute leukemia is an aggressive blood malignancy characterized by the accumulation of pathological hematopoiesis progenitors [27]. Leukemia can be caused by benzene, some chemotherapy drugs classified as alkylating agents, radiation, and the underlying hematological disorders. Acute Myeloid Leukemia (AML) is a disorder caused by abnormal proliferation and differentiation of stem cells that causes an increase in the number of myeloid progenitors in the bone marrow and peripheral blood to produce abnormal granulocytes [28]. Myeloid cells in AML continue to be produced, but cell maturation does not occur, so many abnormal cells are formed. This causes the cumulation of leukocytes in the bone marrow that negatively impacts the function of platelets and red blood cells.

Changes in the normal maturation procedure of precursor cells are caused by the translocation of chromosomes t(8; 21) on a core-binding factor of AML or t(15; 17) on Acute Promyelocytic Leukemia (APL), which produces PML-RARA and chimeric proteins (RUNX1-RUNX1T1). Several studies classify various mutations associated with AML. Class I mutations must coincide with class II mutations so that leukemia can occur. Class I mutations include internal tandem duplications/ITD), c-KIT, FLT3, K/NRAS, TP53, and Tyrosine Kinase Domain mutations/TKD). In addition, there is the role of signal transducer and activator of transcription 3 (STAT3) in stimulating cell proliferation and survival. Class II mutations include CEBPA and NPM1. Mutations of genes related to DNA methylation, IDH-1/IDH-2, TET2, and DNMT3A, were detected in 40% of AML cases, known as class III mutations. C-KIT mutations are related to t (8; 21) or inv (16), whereas NMP1 (class II mutations) often occur together with class I FLT3-ITD mutations or epigenetic mutations of IDH-1, IDH-2, and DNMT3A [29].

AML cells can escape immune attacks through biochemical mechanisms that cause deactivation of cytotoxic lymphoid cells by AML cells. AML cells have the capability for expressing surface proteins, including ligands of cytotoxic T-cell antigen 4

(CTLA4), receptor ligands (PD-Ls) 1 and 2, and programmed death-1 (PD-1). PD-Ls 1 and 2 interact with PD-1 on the surface of lymphoid cells and cause helper T cells to stop forming IL-2 needed for CTC and N.K. cell activation. This results in the inactivation of CTC and N.K. cells, causing these cells to lose the potential to kill AML cells. AML also expresses the neuronal receptor latrophilin 1 (LPHN1). LPHN1 is usually expressed in hematopoietic stem cells and disappears after maturation. LPHN1 in AML simplifies Tim-3-galectin-9 exocytosis so that cells can survive. Galectin-9 interacts with CTC and N.K. cells, causing a reduction in N.K. cell cytotoxic activity and CTC killing. N.K. cells will produce interferon-ɣ (IFN-ɣ) and induce IDO1 activation (indoleamine 2,3-dioxygenase). Formil-L-kynurenine will be degraded to L-kynurenine, which damages N.K. cytotoxic activity. IFN-ɣ also affect the induction of the PD-Ls which can increase the protection capability of AML cells from immune surveillance [30].

Manifestations of COVID-19 in patients without and with leukemia

The incubation period of COVID-19 can be up to 3-14 days, five days on average [31]. During the initial phase, it does not show any symptoms, and the blood tests show normal or slightly decreased leukocyte and lymphocyte count. SARS-CoV-2 will spread to the lungs, digestive system, and heart. Those tissues express ACE2, which plays a significant role as host cells receptor for SARS-CoV-2. Coronavirus spreads through blood and causes the common COVID-19 symptoms, such as productive cough, difficulty breathing, fever, nasal congestion, sore throat, hemoptysis, and diarrhea [32-36]. Most patients' peak temperatures are between 38,1-39°C and mostly show respiratory symptoms [32].

If the disease is left untreated, the disease course may cause uncontrolled inflammatory processes leading to complications such as Acute Respiratory Distress Syndrome (ARDS) and sepsis that can result in death [7]. From initial symptoms to death, it may take 6-41 days, 14 days on average. The duration depends on the patient's age and immunity status [35]. Patients' CT-Scan show ground-glass appearance in the subpleural regions of both lungs. Other radiographic images show infiltrations in upper lung lobes that are associated with severe dyspnea and hypoxemia [33].

China has reported a leukemia patient presenting with a fever for four days, sore throat, productive cough, and difficulty breathing. Clinical examinations reveal an increase in body temperature, leukocytosis, lymphocytosis, hemoglobin, and thrombocytopenia. CT-Scan images showed an opaque ground glass appearance and a small amount of fluid in the pleural sac. The hematological parameters of leukemia patients can decrease the suspicion of infection since processes cause the increased leukocyte in leukemia [37].

COVID-19 patients with cancer as comorbidity are at higher risk of experiencing severe symptoms requiring more intensive care with a higher mortality rate. Seven out of 18 (39%) COVID-19 patients with cancer as comorbidity required ventilators, and it is higher than COVID-19 patients without cancer comorbidities who have to use ventilators (124 out of 1572 patients (8%)) [38]. Currently, no studies have reported an increased susceptibility to getting infected with SARS-CoV-2 in patients with leukemia.

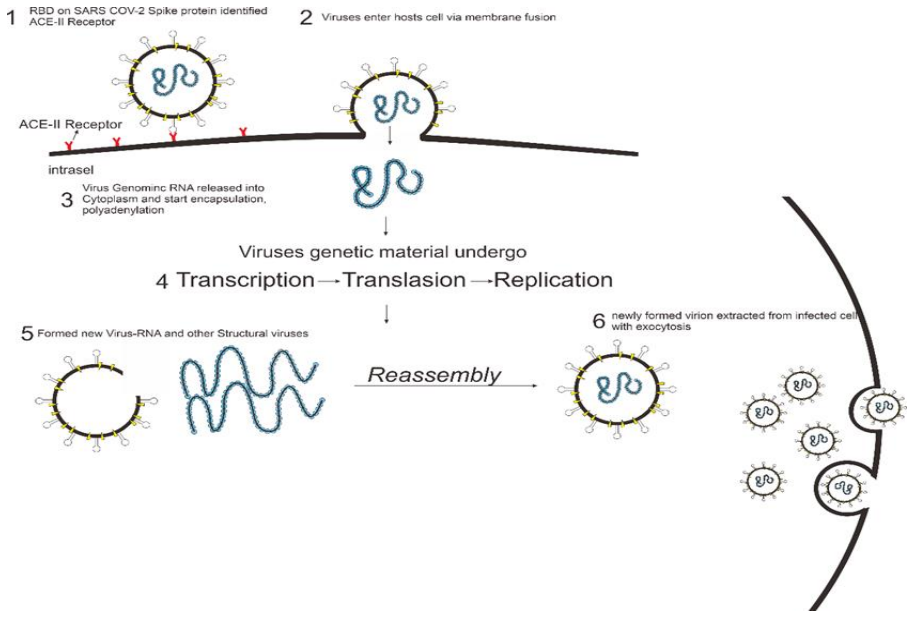

Figure 2. Molecular Mechanism of SARS-CoV-2 Infection. (Taken with Modifications from Koestler, 2020) [39]

Renin-Angiotensin system (RAS) in leukemia mechanism

ACE2, as the host cell receptor for SARS-CoV-2, significantly affects the pathobiology of leukemia. ACE2 is one of the many component molecules of the Renin-Angiotensin System (RAS). In addition to ACE 2, RAS has several other molecules, namely

angiotensinogen (ANGTS), angiotensin receptors (AT1R and AT2R), and AcSDKP. These RAS molecules are found within the bone marrow and compartment cells [40]. RAS has an important role in hematopoiesis, apoptosis, cell proliferation, intracellular signaling, mobilization, angiogenesis, fibrosis in cytokine tissue, and other pathobiologies [41]. Malignant neoplastic blood cells originate from stem cells in pathological proliferative process [40].

Bone marrow RAS plays a role in embryonic hematopoiesis and the production of blood neoplasm [42, 43]. Angiotensin II (Ang II) will stimulate type 1 and type 2 angiotensin receptors (AT1/AT2) and then stimulate or inhibit the Janus-kinase-signal activator and transducer of transcription (JAK-STAT) pathway related to activities of hematopoietic cytokines during normal hematopoiesis and neoplastic myeloproliferation [44-46]. In lymphoid and myeloid leukemia, specific mRNA expressions of RAS components were detected [40, 46].

Malignancy and anticancer therapies cause systemic immunosuppressive state in cancer patients [38]. This condition decreases the body's ability to control virus replication and makes the viral shedding process longer [16]. These then lead to cancer patients being more susceptible to infections than people without cancer, and the recovery process takes longer with more severe symptoms [3].

COVID-19 molecular mechanism and immune reaction in patients with leukemia

SARS-CoV-2's molecular mechanism of infection is not currently well known, but it is thought to have similarities with SARS-CoV's mechanisms. The virus can interact with human cells through spike protein (S) for infection to occur. Genome coding and gene expression will occur following the successful interaction, increasing CoV's adaptation to humans as hosts. CoVs often undergo genome change due to recombination, gene change, gene insertion, or deletions, causing extreme events [24].

SARS-CoV enters its host's cell through fusion with the plasma membrane mediated by proteolytic activity of S protein (S2') [47]. glycoprotein spike (S) will bind with cellular receptor ACE2 and CD209L (lectin type C or L-SIGN) [48]. Aside from membrane fusion, SARS-CoV also enters the host's cell through clathrin-dependent and clathrin-independent endocytosis [49]. SARS-CoV's S protein has a receptor-binding domain (RBD) that recognizes ACE2 as the host cell's receptor [50-54]. Other researches show that the host's ACE2 affinity determines the host's susceptibility to SARS-CoV infection to RBD [55-59].

The RNA genome is released into the cytoplasm after successfully entering the cell. RNA genome will then undergo encapsulation and polyadenylation, then coding some structural and non-structural polypeptide genes [16-24]. RNA genome and virus proteins are then reassembled in virion form in the endoplasmic reticulum and the Golgi. Further, the genome is transported by vesicles that are going to fuse with the plasma membrane [60]. Next, infected cells will release virions via exocytosis. Released viruses can infect kidney, liver, digestive system cells, and T lymphocytes of the respiratory tract, causing signs and symptoms of COVID-19 [61].

Antigen will then be presented to Antigen Presentation Cells (APC), the antiviral immunity center [13]. The antigen peptide presented by Human Leukocyte Antigen (HLA) or Major Histocompatibility Complex (MHC) and will be recognized by virus-specific Cytotoxic T Lymphocyte (CTLs) [13]. SARS-CoV antigen presentation depends on the assistance of MHC 1 and MHC II molecules. Previous studies have shown that some HLAs are related to susceptibility to SARS-CoV, including HLA-Cw * 0801, HLA-B * 0703, HLA-DR B1 * 1202, and HLA-B * 4601. Additionally, the HLA-Cw1502, HLA-A * 0201, and HLA-DR0301 allele are associated with protection against SARS infection. It is also shown that polymorphism of the Mannose-Binding Lectin (MBL) gene related to antigen presentation is linked to the risk of SARS-CoV infection [61-64].

Antigen presentation will stimulate cellular and humoral immunity mediated by B cell and T cell [60]. Immunoglobulin G (IgG) and immunoglobulin M (IgM) are specific antibodies against SARS-CoV; both can be recognized in two weeks, reaching their peaks in 60 days and remaining up to 180 days after infection [65]. SARS-CoV can create irregularity in T cell antivirus response due to T cell apoptosis stimulation, resulting in a decrease of the immune system. Recent reports indicate that in some patients infected with SARS-CoV-2, there is a decrease in CD8 and CD4 T cells in their peripheral blood. CD8 and CD4 memory T cells survive up to 4 years in individuals recovered from SARS and can perform cell T proliferation, DTH response, and IFN-gamma production [66].

The increase of ACE2 level in leukemia causes the host's receptor for SARS-CoV to increase, leading to the hypothesis that patients with leukemia, especially the myeloid type, have higher risks of getting COVID-19, and it can be fatal **(Figure 3)**.

The most common complication of COVID-19 is ARDS. It is generally the main reason for death in patients with COVID-19 [13]. Cytokine storm, one of the many mechanisms causing ARDS, is an uncontrolled systemic inflammatory response caused by the release of chemokines (CCL2, CCL3, CCL5, etc.) in a large number by effector immune cells and pro-inflammatory cytokines (TNF-a, IL-18, IL-12, IL-6, IL-1b, IFN-g, IFN-a, etc.) during SARS-CoV infection [67-70]. Cytokine storm will trigger a massive immune system attack on the body, resulting in many organ failures leading to death in severe SARS-CoV infection cases [70].

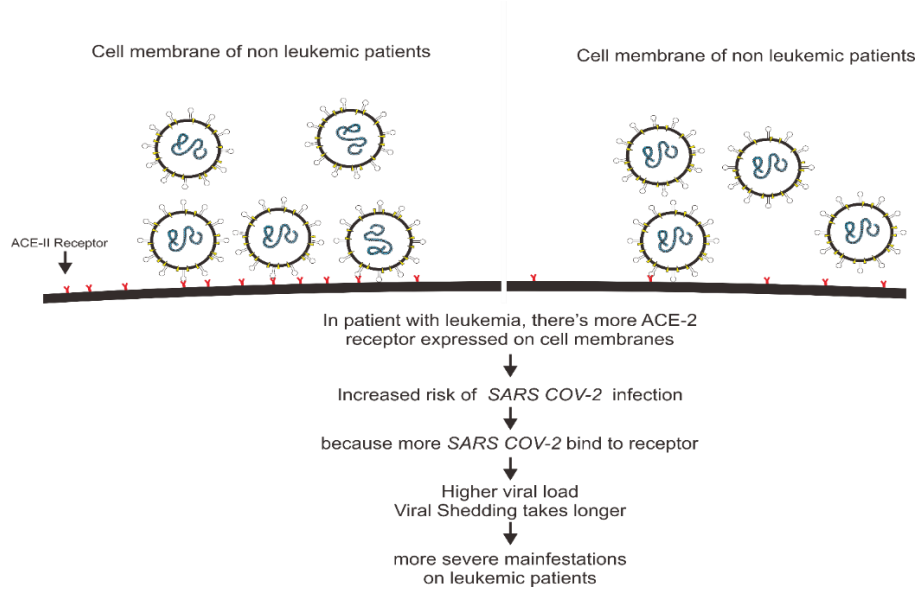

Figure 3. SARS-CoV-2 Infection on Patients with Leukemia

Conclusion

Patients with myeloid leukemia are more susceptible to be infected by SARS-CoV-2 because there are more ACE2, the receptors for SARS-CoV-2, in their bodies. ACE2 plays a role in myeloid malignant hematopoiesis. Viral shedding in patients with systemic immunosuppression, as in leukemia, takes longer. Therefore, the symptoms caused will be more severe in leukemia patients compared to patients without systemic immunosuppression.

Recommendation

It is highly recommended for patients to get COVID-19 vaccination when it is available. In the middle of this pandemic, prevention is necessary for patients with leukemia. All they need to do is maintain personal and environmental hygiene and keep the physical distancing.

A hematologist who will provide therapies such as chemotherapy or bone marrow transplantation is best if the SARS-CoV-2 tests are done on the patients first. If the tests are not available, testing can be done by screening and through chest C.T. imaging. If the test confirms that the patient is infected with SARS-CoV-2, the doctor should consider delaying systemic therapy if possible. Medications for leukemia that do not cause immunosuppression can be continued without any adjusting the dose.

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Conflict of interest: None

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Ethics statement: None

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