# SARS COV-2 Infection in Children with Leukemia

## Lösemili Çocuklarda SARS COV-2 Enfeksiyonu

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## ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) directed great attention and anxiety all over the world. Epidemiologic models predict that the current COVID-19 pandemic will last several months or even several years, until the development of a vaccine and/or herd immunity. Although the course of the infection is often not severe in children, it can be life threatening especially in immunocompromised children with leukemia. Hematopoietic and lymphoid cancers are accounting for approximately 40% of all childhood cancers. The five-year survival rate for childhood cancer has approached to 70% and more than 80% for leukemia in our country. During COVID pandemic, children with leukemia may also have COVID-19 infection, especially when their bone marrow is depressed due to chemotherapy. It is observed that factors such as the underlying type of cancer, status of remission, or having stem cell transplantation may affect the prognosis. As well as standard and proven treatments for febrile neutropenia, all tests and treatments should be applied very quickly and properly for COVID 19 as is all suspected patients. These efforts may contribute to increase the survival of our children with cancer. Given the absence of data to address concerns related to SARS-CoV-2 infection while on chemotherapy, questions are increasing about the approach for management of systemic immunosuppressive therapies, i.e. ceasing or reducing the immunosuppressive medications in children with leukemia.

The current rapid worldwide spread of COVID-19 necessitates identifying optimal preventive strategies and effective medical management. In this report, we tried to review appropriate literature-based approaches for prevention, diagnosis and management of treatment protocols for children with cancer during the pandemic period.

**Key Words:** Children, Medical Management, Leukemia, SARS COV-2 Infection

## ÖZ

Şiddetli akut solunum sendromu koronavirüs 2 (SARS-CoV-2) tüm dünyada dikkatle ve kaygıyla izlenmektedir. Epidemiyolojik modeller, mevcut COVID-19 pandemisinin bir aşı ve / veya sürü bağışıklığı gelişene kadar birkaç ay hatta birkaç yıl süreceğini tahmin etmektedir. Çocuklarda COVID-19 enfeksiyonu genellikle hafif seyretmekle birlikte, özellikle bağışıklığı zayıflamış lösemili çocuklarda hayatı tehdit edebilir. Hematopoetik ve lenfoid kanserler tüm çocukluk çağı kanserlerinin yaklaşık %40'ını oluşturmaktadır. Çocukluk çağı kanserlerinde ülkemizde beş yıllık sağkalım oranı %70'e ve lösemi için bu oran %80'e ulaşmıştır. COVID-19 salgını sırasında, lösemili çocuklarda, özellikle kemoterapi nedeniyle kemik iliğinin baskılandığı dönemde, COVID-19 enfeksiyonuna yakalanma riski yüksek olabilir. Altta yatan kanser türü, kanserin remisyon durumu veya kök hücre nakli yapılmış olması gibi faktörler de enfeksiyona cevabı etkileyebilir. Nötropenik ateşli hastalarda, standart ve kanıtlanmış tedavilerin yanı sıra, COVID 19 için şüpheli hastalarda olduğu gibi tüm testler ve tedaviler çok hızlı ve uygun bir şekilde uygulanmalıdır. Bu çabalar kanserli çocuklarımızın hayatta kalma oranını arttırmaya katkıda bulunacaktır. Kemoterapisi devam eden hastalarda SARS-CoV-2 enfeksiyonu ile ilgili verilerin yeterli olmaması nedeniyle, lösemili çocuklar gibi sistemik immünsüpresif tedavileri devam etmesi gereken hastalarda, immünosüpresif tedavinin azaltılması veya ertelenmesi gibi sorulara cevap aranmaktadır.

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***Conflict of Interest /Çıkar Çatışması:*** *On behalf of all authors, the corresponding author states that there is no conflict of interest.*

***Contribution of the Authors / Yazarın Katkısı: YAZAL ERDEM A:*** Constructing the hypothesis or idea of research and/or article.Reviewing the article before submission scientifically besides spelling and grammar. Taking responsibility in the writing of the whole or important parts of the study. ***OZBEK NY:*** Constructing the hypothesis or idea of research and/or article.Reviewing the article before submission scientifically besides spelling and grammar. Taking responsibility in the writing of the whole or important parts of the study.

***How to cite / Atıf Yazım Şekli :*** Yazal Erdem A, Ozbek NY. SARS COV-2 Infection in Children with Leukemia. Turkish J Pediatr Dis 2020;14(suppl):41-47.

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Received / Geliş tarihi : 28.05.2020
Accepted / Kabul tarihi : 20.07.2020
Online published : 27.07.2020
Elektronik yayın tarihi
DOI: 10.12956/tchd.743711

COVID-19'un dünya çapında hızla yayılması, hastalıktan korunmak için gerekli stratejilerin ve etkin tıbbi tedavilerin geliştirilmesinii gerektirmektedir. Bu yazıda pandemi döneminde lösemili çocuklarda gelişebilecek COVID-19'un önlenmesi, tanı koyulması ve enfeksiyon geliştiğinde tedavi protokollerine yönelik literature dayalı uygun yaklaşımları derlemeye çalıştık.

**Anahtar Kelimeler:** Çocuklar, Tıbbi Tedavi, Lösemi, SARS COV-2 Enfeksiyonu

## INTRODUCTION

In March 2020, World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) pandemic, which is caused by a new virus, namely severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). Thereafter, a rapid increase in the number of patients and deaths due to this disease directed great attention and anxiety all over the world. Since morbidity and mortality of the disease is higher among adults, especially elders, limited reports have analyzed pediatric patients infected with SARS-CoV-2 (2). From the case series, it appears that children have milder clinical symptoms compared to adults, and are less commonly affected by SARS-CoV-2 (3-9). Nevertheless, that could also mean that children might not be tested for SARS-CoV-2 as frequently as adults. Risk factors for the disease have been defined at the beginning of pandemics, particularly among elderly. However, new signs and symptoms such as COVID-eye, and COVID-toe are still including in the diagnostic list (10-12). Fairly or uncontrolled medical conditions, such as chronic lung disease or moderate to severe asthma, serious heart conditions, severe obesity, diabetes, chronic kidney disease undergoing dialysis, and liver disease are among the risk factors for morbidity and mortality (13-14). Besides, immune compromised conditions, including cancer treatment, bone marrow or solid organ transplantation, and congenital or acquired immune deficiencies, have been associated with increased risk of complications from SARS-CoV-2 infection (14-16). Chinese Center for Disease Control and Prevention Report declared the overall case-fatality rate as 2.3% that was higher among those with preexisting comorbid conditions, and 5.6% for patients with cancer (17,18). Epidemiologic models predict that the current COVID-19 pandemic will last several months or even several years, until the development of a vaccine and/or herd immunity (19).

Although the course of the infection is often not severe in children, it can be life threatening especially in immunocompromised children with leukemia. Given the absence of data to address concerns related to SARS-CoV-2 infection while on chemotherapy, questions are increasing about the approach for management of systemic immunosuppressive therapies, i.e. ceasing or reducing the immunosuppressive medications in children with leukemia.

### Aim

There are limited pediatric case reports and case series concerning children with leukemia and COVID-19. However, the epidemiological and clinical patterns of the disease in pediatric patients remain uncertain despite the worldwide spread. In this report, we aimed to review on SARS-CoV-2 infection in children with leukemia in order to provide proposals for the prevention and management of COVID-19 in this population.

### Children with Leukemia

According to the collaborative report of Turkish Pediatric Hematology Association (TPHD) and Turkish Pediatric Oncology Group Association (TPOG), the five-year survival rate for childhood cancer has approached to 70% and more than 80% for leukemia in our country (20). Hematopoietic and lymphoid cancers are accounting for approximately 40% of all childhood cancers. Cancer patients are vulnerable to certain infections as well as to COVID-19. It is observed that factors such as the underlying type of cancer, status of remission, or having stem cell transplantation may affect the prognosis (21-23).

During COVID pandemic, children with leukemia may also have COVID-19 infection, especially when their bone marrow is depressed due to chemotherapy. As well as standard and proven treatments for febrile neutropenia (broad-spectrum antibiotic, supportive treatments), all tests and treatments should be applied very quickly and properly for COVID 19 as is all suspected patients. These efforts may contribute to increase the survival of our children with cancer.

Individuals affected by cancer are more susceptible to infections due to coexisting chronic diseases, overall poor health status, and systemic immunosuppressive states caused by both cancer and anticancer treatments. Leukemia itself may be developed on the background of an immune deficiency, furthermore cancer treatment may itself result in secondary immune deficiency. Immune system dysfunction in patients with leukemia is mostly related to systemic immunosuppressive therapies rather than the malignancy itself, including impaired humoral antibody responses and cell-mediated immunity, qualitative and quantitative phagocytic defects, and disruption of cytokine release. In addition, malnutrition, antibiotic therapy, impairment of mucosal membrane barriers provide ready access for endogenous microbiological flora and other opportunistic pathogens (24,25).

In practice, patients with leukemia who have an infection are generally classified as neutropenic and non-neutropenic. Degree and duration of neutropenia is the most important and readily available measurement of susceptibility to infection. Neutropenia with a neutrophil count ≤0.5x109/L is a serious risk factor for infection. Profound neutropenia is defined as

an absolute neutrophil count ≤0.1x109/L and prolonged neutropenia is defined as neutropenia lasting >7 days. They are both related to the frequency and severity of the infection. To assess the risk of susceptibility to infection, the status of the primary disease such as remission-induction, remission or relapse, the treatment phase should also be considered. Beyond neutropenia, leukemic children may also have impaired cell-mediated immunity (25). The number and percentage of CD4+ T lymphocytes are used as a measure of susceptibility to opportunistic infections (26). In children with leukemia, chemotherapeutics, irradiation, and malnutrition, usually diminish T-lymphocyte activity. (25).

There are many viruses that can result in infections in pediatric cancer patients. Respiratory viral infections can cause significant morbidity and mortality. Viral infections are typically not life threatening in those who are receiving less intense therapy. However, certain viruses such as Herpesviruses, Cytomegalovirus, and Ebstein Barr virus may cause serious infection and mortality in the most intensively treated children, especially in children with acute myeloid leukemia and those who had hematopoietic stem cell transplant (27).

**COVID-19 in Patients with Cancer**

After the beginning of COVID-19 pandemic, limited reports released concerning pediatric patients among many publications. Although there are reports stating that children at all ages are susceptible to COVID-19, clinical manifestations has been less severe compared to those in adult patients. Children under the age of three years or children with underlying conditions, such as impaired lung function, immunosuppression or heart disease are the most frequently affected groups (2,3,17).

Studies, including mostly adult patients, have been stated that cancer patients with COVID-19 infection who admitted to the intensive care unit (ICU) were approximately 1-2% in Wuhan, China; 6% in New York City, USA, and 8% in Lombardy, Italy (28-33). A recent report from Italy revealed that 20% of all deaths from COVID-19 were in patients with active cancer (34). A multi-center study, comprising 105 cancer patients and 536 age-matched non-cancer patients (median age 64 years) who were confirmed with COVID-19, revealed that patients with cancer had higher risks in all severe outcomes. Among them, patients with hematological cancer, lung cancer, or metastatic cancer disclosed severe events more frequently compared to those in non-cancer patients. However, non-metastatic cancer patients experienced similar frequencies of severe conditions compared to those observed in patients without cancer. Patients who received surgery for cancer treatment had also higher risks of having severe events, while patients who had only radiotherapy did not demonstrate significant differences in severe events when compared to patients without cancer (22). According to this report, patients who had severe types of cancer or had intensive treatment modalities appear to be more susceptible to COVID-19 complications. A report by Liang et al. (35) included 18 elderly patients (mean age 63 years) with heterogeneous cancer diagnosis. The report revealed that patients who underwent chemotherapy or surgery in the past month had higher risk (39% vs 8%) of clinically severe events (being admitted to the ICU, requiring invasive ventilation, or death) compared to those who did not receive those treatments. A cohort study at two centers in Wuhan revealed that among 128 hospitalized adult patients with hematological cancers, 13 (10%) developed COVID-19. Subjects with hematological cancer and COVID-19 appeared to have more co-infections including bacteria, fungi and other viruses. They reported hospitalized patients with hematological cancers have a similar case rate of COVID-19 compared with normal health care providers, but have more severe disease and a higher case fatality rate, related predominately to bacterial coinfections. Those patients with hematological cancer, who were symptomatic, had significantly decreased hemoglobin, lymphocyte count, lymphocyte subset, and platelet count; and higher concentrations of D-dimer (36).

An analysis of 334 adult patients with cancer from USA accounted 6% of patients diagnosed with COVID-19. Cancer patients under age 50 had a fivefold higher mortality rate than those in this age group without cancer (37). In another report from USA, case fatality rate was found to be 37% for hematologic malignancies, and 25% for solid tumors (38). Boulad et al. (39) conducted a research in 120 asymptomatic pediatric patients with cancer, without known exposure and symptoms. They found that the rate of SARS-CoV-2 positivity was only 2.5% and they observed a 14.7% rate of SARS-CoV-2 positivity in their asymptomatic caregivers. Only one patient with COVID-19 required hospitalization, all other children were managed at home. They suggested that pediatric patients with cancer may not be more vulnerable to SARS-CoV-2. However, unrecognized SARS-CoV-2 infection in asymptomatic caregivers is an important problem for the control of infection. A major survey on SARS-CoV-2 infections in pediatric patients on anti-cancer treatment including patients from 25 countries disclosed that only nine patients were stated positive for COVID-19. Eight of them had asymptomatic to mild disease (40).

**Infection Control Measures in Centers Caring for Cancer Patients**

In Turkey, Public Health General Directorate of the Ministry of Health, published guidelines for current pandemic for both public and health care professionals (41,42). Furthermore, in recognition of the need to protect health workers and high-risk patients, infection control measures in centers caring for cancer patients were also settled to reduce the exposure of patients and staff member to possible infection with COVID-19.

In addition to the strict measures, in the early period COVID hospitals and COVID care services have been established. According to these guidelines, patients and their relatives should be informed about COVID-19 symptoms and prevention methods. General preventive measures (social distancing, hand washing, limiting the exposure to other people, covering a facemask) are obligatory rules. Patients and their relatives should be questioned for symptoms and signs of COVID-19 prior to admission to outpatient chemotherapy units. If possible, immunosuppressed children should be isolated from other pediatric patients. They should also warn off using public transport and visiting crowded areas.

The outpatient visits of the patients should be reduced as much as possible in order to decrease new infections. Less frequent controls for stable patients could be recommended, and the control of patients who are under follow-up in remission should be postponed according to the decision of attending physician. Radiological examinations should be delayed in this period; especially ultrasonography carries high transmission risk due to contact (43). Health professionals should separate into teams, by working on alternate days or weeks and not sharing offices and common areas, in order to avoid infection or preventative quarantine in the whole staff in the same period (44,45). Clinical and outpatient application, and the attendant should be limited in number. To minimize face-to-face visits, telephone calls or digital platforms could be implemented in practice during the pandemic for visits and screening COVID-19 symptoms or for sustainable new models of cancer care, where available. Telehealth may provide contribution for patients living in remote areas or could be used for meetings with colleagues, particularly multidisciplinary tumor boards, as well as patient consultations.

If possible, each hospitalized patient should be placed in a single negative pressure room. Nebulizers, oxygen masks or nasal continuous positive airway pressure systems should not be used on an open ward (46,47). Aerosol-generating procedures such as intubation and bronchoscopy increase the risk of viral transmission and nosocomial transmission of COVID-19 is one of the important main challenge (48). In order to continue the treatment of cancer patients without interruption and prevent infection transmission, staff (physician, nurse, secretary, cleaning staff) working in chemotherapy and/or radiotherapy departments should not be assigned to other units and the number of working personnel should be limited. The healthcare workers should take standard, contact and droplet isolation measures. The use of gloves, masks, glasses, bones and gowns, is essential for safe care of patients and healthcare workers to reduce risks of transmission on pediatric hematology-oncology units. The personal protection equipment are also recommended during clinical visits. People visiting the patient visit should be limited in number. All the doctors and patients in hematology-oncology units should be tested every week (49). If a patient undergoing chemotherapy and / or radiotherapy is found to be positive for COVID-19, necessary isolation measures should be taken, and the decision to continue, stop or delay in oncological treatment should be made by the oncology physician (45,50).

**Treatment in Immunocompromised Patients**

The decision to begin and continue cancer treatment during this crisis is challenging given the risk of death from cancer versus death or serious complications from SARS-CoV-2. In patients with suspected COVID-19 infection, it may be recommended to start and continue cancer treatment. However, the decision to start treatment in newly diagnosed patients should be considered after careful evaluation of the goals of the treatment, the general condition of the patient, the ability to tolerate treatment, and the risk of COVID-19 infection (51,52). It is advisable to obtain an informed consent from parents and adolescent patients with leukemia and COVID-19 before treatment (53). Induction treatment for patients with cancer, scheduled chemotherapy should not be delayed or interrupted unless COVID-19 is suspected or diagnosed. In case of leukemia patient tested positive for SARS-CoV-2 infection, immunosuppressive cancer therapy should be postponed. There are no accepted international guidelines and consensus to answer when can cancer treatment be safely restart after the diagnosis of COVID-19. It is recommended for most patients, to stop immunosuppressive therapy until symptoms from COVID-19 have improved. Chemotherapy could be restarted once symptoms were improved and after two sequential negative tests after 24 hours apart obtained. Balancing the risk/benefit ratio should be done in rapidly progressing cancers, and initiation of cancer treatment must be individualized (54-58).

As SARS-CoV-2 has an incubation period of 2–7 days, it can be recommended a treatment delay of no more than 7 days to allow a brief period of observation to screen for COVID-19 in suspected children. Some authors recommend no more than 7-day-delay in the consolidation phase and intermediate phase of chemotherapy and no more than 14 days in the maintenance chemotherapy for patients in the remission phase with acute lymphocytic leukemia and acute non-lymphocytic leukemia. It is also advised to interrupt the treatment in infected patients with leukemia, until two negative results will be obtained (51,57).

In case of patients diagnosed with COVID-19, patients whose disease is in remission, COVID-19 should be treated first. For children who are not in remission, they should be treated for COVID-19, and chemotherapy for the primary disease should be temporarily delayed or reduced according to the patient's situation (54-57). The increase in the maximum delay before chemotherapy strikes a balance between the potential risk of SARS-CoV-2 infection and tumor recurrence.

According to the literature, timing of surgery and/or radiation schedules may be altered, and major surgeries should be

postponed or cancelled (50). International radiation oncology groups recommends for alternative radiation treatment schemes. In case of radiotherapy is required, hypofractionation (ie, by increasing the dose per fraction while reducing the number of daily treatments) should be considered to maintain clinical efficacy and safety (59).

Cancer patients with fever should be tested also for COVID-19, and comprehensive usual evaluation should be performed for alternative causes of fever in patients with febrile neutropenia. During the influenza season, it is reasonable to test for influenza together with SARS-CoV-2 testing. If a patient with leukemia has symptoms that may be related to COVID-19, the treatment for COVID-19 should be started immediately at hospital. In this situation, waiting to obtain the polymerase chain reaction result would be late. Early empirical treatments are very critical for immunocompromised children with fever. Since it is known that immunocompromised patients may have prolonged viral shedding, treatment duration may also be extended (60,61). Supportive care should be provided early to relieve symptoms. To date, no specific and effective antiviral treatment recommended for COVID-19 is available. Potential drugs, which are in clinical use for adults, have not been tested systematically in children, and clinicians are waiting for the results of clinical trials testing the efficacy of these drugs in children.

### Blood Products

There may also be problems with transplant products and transfusion. Viral shedding from the respiratory system in the blood plasma or serum is common with coronaviruses (62). The risk for SARS-CoV-2 transmission through blood components in asymptomatic SARS-CoV-2 infected individuals is yet to be established. This problem could be overcome through improving blood biosafety protection, following standard measures for the virus inactivation in blood products, and questioning the health condition of blood donors and their relatives for a period after donation (63,64). In addition, we observed that, during COVID-19 the blood donor pool and blood supplies reduced due to the hesitation of donors.

## CONCLUSION

COVID-19 is a new and serious pandemic, that has spread rapidly with a critical impact on hematology-oncology practice. Data is limited in childhood leukemia, but suggest that, management of cancer therapy during the pandemic is challenging given the higher morbidity and mortality rate in immunocompromised patients, especially if they recently received myelosuppressive chemotherapy and have comorbid medical conditions. The current rapid worldwide spread of COVID-19 necessitates identifying optimal preventive strategies and effective medical management. A clear understanding of the underlying immune response to SARS-CoV-2 infection will facilitate the development of effective treatments and vaccines to control the ongoing pandemic. Cancer clinicians and patients are critically affected and need guidance from experts and colleagues regarding reasonable changes to standard practice. We tried to review appropriate approaches for prevention, diagnosis and treatment protocols for children with cancer during the pandemic period.

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