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Original Article

COVID-19 Infection in Children with Leukemia: A Single-center Retrospective Study

Lösemili Çocuklarda COVID-19 Enfeksiyonu: Tek Merkezli Retrospektif Çalışma

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ABSTRACT

Objective: Children were less likely than adults to develop severe illness from coronavirus disease-2019 (COVID-19) infection, whereas children with leukemia had compromised immunity and may be at increased risk of severe COVID-19 infection. The aim of this study is examine the characteristics and outcomes of COVID-19 in children with leukemia.

Method: Between March 2020 and February 2021, patients on active leukemia treatment who were diagnosed with severe acute respiratory syndrome coronavirus-2 infection were enrolled in the study. Clinical, laboratory, and radiological characteristics, as well as infection severity and prognosis, were all assessed.

Results: The children's median age was 9.6 years, and 66.7 percent of them were male. The majority of patients with COVID-19 infection were in the early stages of leukemia treatment and had severe or critical COVID-19 infection. Six patients were treated for COVID-19. Five patients required oxygen, six were in the intensive care unit, and three were intubated. Twelve patients were fully recovered, and three died. Two of the patients were re-infected with COVID-19. The disease status of re-infected patients was worse than the first infection, and the duration of polymerase chain reaction positivity was much longer.

Conclusion: Children with leukemia who have COVID-19 infection may have severe/critical illness. The type and character of primer malignancy, as well as the prognostic factors of COVID-19 infection, may all have an impact on clinical outcomes. It is critical to take the most stringent precautions to prevent infection from spreading to these patients.

Keywords: Children, COVID-19, leukemia, severity, prognosis

ÖZ

Amaç: Çocukların koronavirüs hastalığı-2019 (COVID-19) enfeksiyonundan ciddi hastalık geliştirme olasılığı yetişkinlerden daha düşükken, lösemili çocukların bağışıklığı zayıf olması nedeniyle ciddi COVID-19 enfeksiyonu geçirme riski daha yüksek olabilir. Bu çalışmanın amacı, lösemili çocuklarda COVID-19 enfeksiyonu özelliklerini ve prognozunu incelemektir.

Yöntem: Mart 2020 ile Şubat 2021 arasında aktif lösemi tedavisi gören ve şiddetli akut solunum yolu enfeksiyonu sendromu-koronavirüs-2 enfeksiyonu tanısı alan hastalar çalışmaya alındı. Klinik, laboratuvar ve radyolojik özelliklerin yanı sıra enfeksiyon şiddeti ve prognozu da değerlendirildi.

Bulgular: Çocukların ortanca yaşı 9,6 idi ve yüzde 66,7'si erkekti. COVID-19 enfeksiyonu olan hastaların çoğu lösemi tedavisinin erken aşamalarındaydı. Hastaların çoğunda ciddi veya kritik COVID-19 enfeksiyonu mevcuttu. Altı hastaya COVID-19 için spesifik ilaç tedavisi uygulandı. Beş hastanın oksijen ihtiyacı oldu, altı hasta yoğun bakım ünitesinde takip edildi, bunlarda üçü entübasyona gereksinim duydu. On iki hasta tamamen iyileşti ve üç hasta öldü. İki hastada COVID-19 ile re-enfeksiyon gelişti. Re-enfekte olan hastaların hastalık durumu ilk enfeksiyondan daha kötüydü ve polimeraz zincir reaksiyonu pozitiflik süresi çok daha uzundu.

Sonuç: COVID-19 enfeksiyonu olan lösemili çocuklarda ciddi/kritik hastalığa yol açabilir. Primer malignitenin tipi ve karakterinin yanı sıra COVID-19 enfeksiyonunun prognostik faktörleri klinik sonuçlar üzerinde etkilidir. Enfeksiyonun bu hastalara yayılmasını önlemek için en katı önlemleri almak çok önemlidir.

Anahtar kelimeler: Çocuklar, COVID-19, lösemi, şiddet, prognoz

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INTRODUCTION

The coronavirus disease-2019 (COVID-19) pandemic has affected people of all ages, with children accounting for 1-5% of total number of pediatric patients with infections[1]. The severity and mortality of patients infected with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) were directly related to age[2]. As a result, children were less likely to develop severe illness from COVID-19 infection than adults. Indeed, 16% of them did not show any relevant signs or symptoms, while 1.8% of them required intensive care[3]. Infants and children younger than 5 years old were more likely to develop severe illness than older children due to their smaller age and immaturity of their immune system[4]. The risks for pediatric leukemia patients have not been understood very well. COVID-19 infection was found to be more common in adult cancer patients than in the general population[5-8]. Children being treated for leukemia who have become immune-compromised have been thought to be suffering from a severe illness[9]. In addition, some reports suggested that this was not the case[10]. The aim of this study is to look at the progression of COVID-19 infection in children with leukemia.

MATERIALS and METHODS

Between March 2020 and February 2021, we conducted a retrospective study to examine the characteristics and outcomes of hospitalized leukemia patients with COVID-9 infection. Patients on active anticancer treatment who were diagnosed with SARS-CoV-2 infection via reverse-transcription polymerase chain reaction (RT-PCR) testing of nasopharyngeal swabs were included in the study. The presence of any respiratory or gastrointestinal symptoms or signs in a patient who tested positive for SARS-CoV-2 by RT-PCR was defined as novel COVID-19. The guidelines of Republic of Turkey Ministry of Health (MoH) and World Health Organization (WHO) were used for diagnosis[11,12]. Clinical, laboratory, and radiological characteristics were used to classify infection severity as mild, moderate, severe, or critical according to the WHO and MoH disease severity classification[11,12]. Severe disease was defined based on the presence of dyspnea, central cyanosis, and an oxygen saturation of less than 92 percent. The diagnosis of critical disease necessitated the presence of respiratory failure, sometimes with acute respiratory distress syndrome, shock, and signs of multi-organ failure such as encephalopathy, heart failure, abnormal coagulation, and acute renal failure. Patients were treated according to recommendations of the MoH. Approval for the study was obtained from MoH and Bursa Yüksek İhtisas Training and Research Hospital Clinical Research Ethics Committee (decision number: 2011-KAEK-25 2020/12-19, date: 23.12.2020) and informed consent from parents and/or patients.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 22.0.

RESULTS

Fifteen pediatric leukemia patients had also SARS-CoV-2 positivity. Eleven of them had acute lymphoblastic leukemia (pre-B-ALL: 10, ALL trans pre-B with myeloid markers: 1) and four had acute myeloid leukemia (AML) (M3:2, M4:1, M1:1) (Table 1). The children's median age ranged from 2 to 18 years, with a male preponderance (66.7%). Patients under the age of ten accounted for 66.6 percent of all patients, and the ages of the highest percentage (33.3%) of patients ranged between 9-12 years. The indicated percentages of patients were receiving induction therapy (53.3%), consolidation therapy (40%) or undergoing diagnostic tests (6.6%). Most of the patients with COVID-19 infection (53.3%) were receiving (0-3 months) induction chemotherapy. The patients were asymptomatic or had mild (26.7%), moderate (26.7%), severe (13.3%) and critically severe COVID-19 infection (33.3%). All of the patients who had severe or critically severe COVID-19 infection were in their first 3 month of cancer treatment.

The most common presenting signs were fever in 73% and cough in 33% of the patients, while 7% of the patients were asymptomatic. COVID-19 pneumonia was detected in 93% of the patients and five of them had hypoxemia. Most frequently respiratory system involvement was seen in 93% of the patients, followed by involvement of central nervous system (CNS) (33%), gastrointestinal system (GIS) (27%) cardiovascular system (CVS) (27%), urinary system (20%), musculoskeletal system (7%) and skin (7%). CNS involvement presented with blurred vision in four, altered consciousness in two and cranial infarct in one patient. GIS involvement presented with diarrhea in two, vomiting in one and pancreatitis in one patient. CVS involvement manifested itself with hypotension and shock in four patients (Table 1).

At the time of presentation, laboratory tests revealed neutropenia in 66.6%, lymphopenia in 80%, and thrombocytopenia in 66.6% of our patients. C-reactive protein (CRP) (73.3%), D-dimer (80%), ferritin (93.3%), fibrinogen (20%), and lactate dehydrogenase (LDH)

Table 1. Demographic and clinical characteristics of leukemia patients with COVID-19		
Total number of cancer patients with cancer	**n=15**	**%**
Median age (range) (years)	9.4 (2-18)	
Sex		
Male	10	66.7
Female	5	33.3
Type of cancer		
AML	4	26.6
ALL	11	73.3
Disease status		
At diagnose	1	6.6
Induction	8	53.3
Consolidation	6	40
Diagnosis		
PCR, clinic and radiologic positivity	6	40
PCR positivity only (contact with positive person)	1	6.6
PCR negative, clinic and radiologic positivity	8	53.3
Contact history	9	60
Most frequent symptoms and findings		
Asymptomatic	1	6.6
Fever	11	73.3
Cough	5	33.3
Other respiratory system findings (tachypnea, dyspnea, hypoxemia)	5	33.3
Organs and system involvement		
Respiratory system (upper respiratory tract infection + pneumonia)	14	93.3
Gastrointestinal system	4	26.6
Diarrhea	2	13.3
Vomiting	1	6.6
Pancreatitis	1	6.6
Central nervous system	5	33.3
Blurred vision	4	26.6
Change in consciousness	2	13.3
Cranial infarct	1	6.6
Musculoskeletal system	1	6.6
Skin	1	6.6
Cardiovascular system (Hypotension and shock)	4	26.6
Urinary system	3	20
Radiologic findings		
Normal	1	6.6
Bilateral diffuse or patchy ground glass opacity	5	33.3
Diffuse or patchy pneumonic infiltration or consolidation	7	46.6
Pneumonic infiltration and ground glass opacity	2	13.3
COVID-19: Coronavirus disease-2019, AML: Acute myeloid leukemia, ALL: Acute lymphoblastic leukemia, PCR: Polymerase chain reaction		

(33.3%) levels increased in respective percentages of patients (Table 1). After treatment, CRP and ferritin levels decreased while hemoglobin, white blood cell (WBC), platelet (PLT), and lymphocyte counts increased. Patients coded as P1, P2, and P10 were critically ill children with greatest alterations in laboratory test results (Table 2). COVID-19 infection was discovered after four patients had received steroids as part of their leukemia treatment protocol. Patients suffering from febrile neutropenia received empirical treatment with broad-spectrum antibiotics. Six patients were given hydroxychloroquine, azitromycine, remdesevir, and lopinavir to treat COVID-19 infection. COVID-19 was untreated in nine patients. Mortality rates of patients who did and did not receive COVID-19 treatment did not differ statistically significantly.

The patients were all hospitalized for a median of 17 (6 to 53) days. Five patients (33%) required oxygen treatment. Six patients (40%) were admitted to the intensive care unit (ICU), and three (20%) were intubated (Table 2). Twelve patients recovered completely, and three (20%) patients died. One of the deceased patients had recently been diagnosed with AML, and the other two were in the first and third months of ALL treatment, respectively. AML patient had an intracranial infarct, diffuse intravascular coagulation, and fungal infection (*Candida albicans* was detected in blood culture). After contracting COVID-19 infection, all three patients died of cardiovascular shock. At a median of 11 (2 to 25) days, the PCR tests became negative. Two ALL patients were re-infected with COVID-19, with the second PCR positivity lasting longer than the first (Table 2).

DISCUSSION

The incidence of COVID-19 infection was estimated to be 0.8% in the general pediatric population, 1.3% in pediatric cancer patients, and 2.5% in pediatric oncology patients[13,14]. Children with cancer appear to be more vulnerable to COVID-19 than the general pediatric population.

Our patients' median age was 9.4 years (average 9.6), with the greatest percentage of age range being between 9 and 12 years (33.3%). In our study, as in the literature, there was a male preponderance (66.7%)[15-19].

In our study, a significant difference in the detection rate of COVID-19 infection was found between the patients in the early and late stages of leukemia treatment. The majority of patients (53.3%) who were diagnosed with COVID-19 infection were in the early stages of treatment (0-3 months) which could be related to the patient's weaker immunosuppression status at the start of treatment.

COVID-19 in pediatric patients leads generally asymptomatic, mild, or moderate course[14-21]. In our study, the percentage of patients with severe or critical COVID-19 infection (46.6%) were higher when compared with children having asymptomatic, mild, or moderate COVID-19 infection. The first three months of treatment were found to be the most critical period for pediatric leukemia patients with COVID-19 infection, as all of the patients who had critical or severe disease were in their first three months of treatment.

Most common presenting symptoms of our patients were fever and cough, which was consistent with the findings of COVID-19 infection reported in other cited studies[14-16,17,20-24]. Except for one study[25], other respiratory system findings (tachypnea, dyspnea, and hypoxemia) were more common than those reported in referenced studies[14,15,17,24]. The rates of involvement of the respiratory system were generally comparable to the literature data, whereas the involvement of the CNS and GSI was observed in greater number of our patients than reported in the literature[16,19,20-23]. CNS symptoms were the most common clinical symptoms in our critically ill patients with fatal outcomes. Other referenced studies[13,14,24,25] reported radiologic abnormalities at average incidence rates of 30%, 40%, 50%, and 57%, respectively, whereas radiologic abnormalities were found in 93% of our patients.

Significantly elevated CRP, fibrinogen, D-dimer, LDH, ferritin levels, as well as lymphopenia, thrombocytopenia, and neutropenia, were found in our critically ill patients comparable to those previously reported relevant laboratory values[13,14,17,24,26-29]. Following treatment, there was a decrease in CRP and ferritin levels, as well as an increase in hemoglobin, WBC, PLT, and lymphocyte levels. Patients with the greatest changes in these laboratory variables were generally severely/critically ill (P1, P2, and P10) children with fatal outcomes.

In the largest pediatric case series, more than 90% of children diagnosed with COVID-19 had asymptomatic, mild or moderate disease[30-34]. Children who required intensive care (1.8%) and having higher mortality rate (2.2%) had other underlying diseases [30-34]. Presumably, in pediatric immunosuppressive cancer patients with COVID-19 disease may have much more severe illness than in healthy children [35-37]. The link between immunosuppression and severe COVID-19 disease is not

Table 2. Laboratory characteristics, treatment, hospitalization days and prognosis of patients		
Total number of cancer patients with cancer	**n=15**	**%**
Laboratory findings		
Neutropenia	10	66.6
Lymphopenia	12	80
Anemia	15	100
Thrombocytopenia	10	66.6
CRP (mg/dL) median (range)	16.5 (3-182)	
Increased CRP	11	73.3
D-dimer (Mg/mL) median (range)	1.6 (0.4-35)	
Increased D-dimer	12	80
Ferritin (mL/ng) median (range)	1155 (349-10000)	
Increased ferritin	14	93.3
Fibrinogen (median) (range)	358 (62-694)	
Increased fibrinogen	3	20
LDH (median) (range)	253 (96-608)	
Increased LDH	5	33.3
Severity of disease		
Asymptomatic/mild	4	26.6
Moderate	4	26.6
Severe	2	13.3
Number of hospitalized	15	100
Length of hospitalization (median, range) day	17 (6-53)	
Necessity of intensive care unit	6	40
Necessity of oxygen treatment	5	33.3
Necessity of intubation	3	20
Treatment for COVID-19		
No treatment	9	60
Hydroxychloroquine	2	13.3
Hydroxychloroquine + Azitromycine	1	6.6
Lopinavir	2	13.3
Lopinavir + Remdesevir	1	6.6
Steroid treatment	4	26.6
Length of PCR positivity (median, range) days	11 (2-25)	
Outcome of disease		
Recovery	12	80
Death	3	20
Reinfection	2	13.3
Length of PCR positivity (median, range) at reinfection, days	21 (8-35)	
CRP: C-reactive protein, LDH: Lactate dehydrogenase, PCR: Polymerase chain reaction, COVID-19: Coronavirus disease-2019		

well established. In some studies children who received chemotherapy and immunosuppressive therapy had a mild/asymptomatic disease course and favorable clinic outcomes of COVID-19[13,18,38-40]. COVID-19 appeared to lead a milder course in the immune-compromised pediatric population, possibly due to non-smoking status, the presence of fewer comorbidities, lower expression of ACE2 receptors, and having a higher number of B and T regulator cells, resulting in a "lesser inflammatory" immune response[41,42]. Although the

proportion of children with cancer who had critical illness with progressive respiratory failure and required ICU (8.5-17.6%) was higher than in the general pediatric population[14,17], a systematic review could not find any correlation between COVID-19 disease and an increase in associated mortality in children with cancer. The types of tumors have no effect on the outcome[43]. Children in our study required ICU care (40%), were intubated (20%), and died (20%) at significantly higher rates than those previously reported in the literature[14,17]. These higher rates may be associated with several causative factors as follows: 1) greater number of children in our study had severe/critical (46.6%) COVID-19 disease; 2) the majority of them were still in the early stages of induction treatment; 3) two of three deceased patients had newly diagnosed leukemia with aggressive prognostic factors; and finally all patients had unfavorable prognostic laboratory findings regarding COVID-19 infection (higher CRP, fibrinogen, D-dimer, LDH, ferritin levels, lymphopenia, thrombocytopenia, and neutropenia). The prognosis of all re-infected patients is an important point to be considered in our study. The disease status of re-infected patients was worse relative to those with novel COVID-9 infection with longer duration of PCR positivity.

Study limitation

The limitations of our study are that it is a single-center study and the number of patients is low.

CONCLUSION

As a result, children with leukemia may have severe/critical COVID-19 infection. When diagnosis of leukemia is made, the course of chemotherapy, and the prognostic factors of COVID-19 infection may all become important criteria for clinic outcomes. In these children, extreme caution is required.

Ethics

Ethics Committee Approval: Approval for the study was obtained from MoH and Bursa Yüksek İhtisas Training and Research Hospital Clinical Research Ethics Committee (decision number: 2011-KAEK-25 2020/12-19, date: 23.12.2020).

Informed Consent: Informed consent was received from parents and/or patients.

Peer-review: Internally peer reviewed.

Author Contributions

Surgical and Medical Practices: E.G.K., Concept: E.G.K., Design: E.G.K., Data Collection and/or Processing: D.G., R.Y., Analysis and/ or Interpretation: D.G., R.Y., Literature Search: D.G., Writing: D.G.

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