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Characteristics of COVID-19 in pediatric patients with hematological malignancies

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Abstract

Introduction: As more data is collected, hematologists will be able to gain more insight into the impact of coronavirus disease 2019 (COVID-19) on pediatric patients with hematological malignancies.

Material and methods: We analysed 21 cases of COVID-19 in pediatric patients with onco-hematological diseases treated in the Western Ukrainian Pediatric Medical Center from March 2020 through May 2021. The majority of patients (71.4%) were diagnosed with acute lymphoblastic leukemia. All patients from the analyzed cohort had an asymptomatic, mild or moderate course of coronavirus-19 infection. The most common symptoms of COVID-19 were fever, cough, gastrointestinal symptoms, and dermatitis. Severe severe acute respiratory syndrome coronavirus 2 increased the risk of liver toxicity and venous thrombosis.

Results and conclusion: Our analysis showed that pediatric patients with hematological malignancies need the same treatment approach for COVID-19 as for other infective complications.

Key words: COVID-19, hematological malignancies, immunosuppression, pediatric patients

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Introduction

Children seem to be less at risk than adults of developing a severe form of coronavirus disease 2019 (COVID-19), but the specific risk in pediatric patients with hematological malignancies is not yet understood [1]. While cases with COVID-19 and asymptomatic severe severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) positive tests have been documented in children with acute lymphoblastic leukemia (ALL), the general observation is that most patients clear their infections with few complications. However, there have been serious cases of COVID-19 associated with mortality [2, 3].

Mortality in COVID-19 patients has been linked to the presence of the so-called 'cytokine storm' induced by the virus. Excessive production of proinflammatory cytokines leads to widespread tissue damage, resulting in multiorgan failure and death [4]. The healthy host's immune response to the SARS-CoV-2 virus is hyperactive, resulting in an excessive inflammatory reaction. Many who die from COVID-19 suffer hyper-inflammation with features of 'cytokine storm' syndrome [5].

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In addition, a serious condition that appears to be linked to COVID-19 is multisystem inflammatory syndrome in children (MIS-C). In children who go on to develop MIS-C, some organs and tissues, such as the heart, lungs, blood vessels, kidneys, digestive system, brain, and skin, become severely inflamed. This appears to be an excessive immune response related to SARS-Cov-2 [6]. Some patients with COVID-19 benefit from immunosuppression [7, 8].

However, it is unclear whether the risk of COVID-19 may be higher or lower in pediatric patients with hematological malignancies due to treatment-induced immunosuppression. The major threat to children with oncohematological diseases when they acquire COVID-19 is the malignancy itself [9]. Chemotherapy may have to be delayed if the patient tests positive for SARS-CoV-2. Delays in treatment may lead to increased morbidity and mortality. The questions of when to treat, when to wait, and how long to wait remain unanswered. For patients in advanced stages of the disease, the real benefit of the treatment in the context of the risk of COVID-19 must be considered [10].

Ukraine is currently fighting the pandemic and has recorded nearly 5 million cases of COVID-19 and 113,000 deaths. As more data is collected, we will be able to gain more insight into the impact of COVID-19 on pediatric oncology and hematology.

The aim of our study was to find common health problems caused by SARS-CoV-2 in a group of patients with oncohematological diseases.

Material and methods

This was a retrospective study of medical records of pediatric patients with hematological malignancies who tested positive for SARS-CoV-2. Data regarding age, sex, clinical symptoms, and results of laboratory and instrumental investigations were collected. Statistics Version-8 was used for data analyses.

Results

We analyzed 21 cases of COVID-19 in pediatric patients with hematological malignancies treated in the Western Ukrainian Specialized Pediatric Medical Center from March 2020 through May 2021, with 24 months of follow up. 15 patients (71.4%) were diagnosed with ALL, four (19%) with acute myeloid leukemia (AML), one (4.7%) with non-Hodgkin diffuse lymphoblastic lymphoma (NHL), and one (4.7%) with Langerhans cell histiocytosis (LCH). The majority of patients were treated for ALL; 14 of them (93%) were in remission and one patient (6.6%) was diagnosed with leukemia during the treatment of COVID-19 infection. Four patients with ALL (26.6%) were included in the high-risk group and treated with a high-dose intensive program of chemotherapy. Seven patients (46.6%) from the intermediate risk group were on non-intensive chemotherapy, and four patients (26.6%) were on maintenance therapy.

Two patients with AML (50%) in their first remission were on maintenance chemotherapy. One girl (25%), in her first early isolated bone marrow relapse of AML, was treated with high-dose intensive chemotherapy, and one child (25%) was in the second long-lasting remission status after allogeneic hematopoietic stem cell transplantation. Patients with NHL and LCH were on a maintenance chemotherapy program.

The sex ratio in our patient cohort was 2:1 M:F: 14 boys (66%) and seven girls (33%). The median age of patients with a positive SARS-CoV-2 test was 7 years (range: 2–16). The A(II)Rh(+) blood group was the most common found in patients (33.3%). 81% of COVID-19 cases were diagnosed with reverse transcription polymerase chain reaction (RT-PCR) tests, and 19% via serological tests. SARS-CoV-2 positivity remained for a median of 19 days (range: 7–67).

12 SARS-CoV-2 positive patients (57%) were treated at home, while nine (43%) were hospitalized for a median 15 days (range: 7–30).The vast majority of patients (76%) had mild SARS-CoV-2 infections, 19% were asymptomatic, and one (4.7%) was diagnosed with moderate severity bilateral pneumonia. The most common symptoms of COVID-19 were fever (76%), rhinitis and cough (57%). In 19% of patients, COVID-19 manifested with gastrointestinal symptoms (abdominal pain, diarrhea), 14.3% had skin manifestations (urticarial, maculopapular rash), and 4.7% had anosmia.

It is difficult to interpret the results of laboratory investigations of the patients from the analyzed cohort because they were treated with chemotherapy of differing intensities and this had a severe impact on the laboratory results. The level of hemoglobin ranged from 61 g/L to 137g/L (median 104 g/L), the level of platelets from 33 × 10^9/L to 872 × 10^9/L (median 223 × 10^9/L), the level of leukocytes from 0.07 × 10^9/L to 6.7 × 10^9/L (median 3.2 × 10^9/L), the level of neutrophils from 0% to 88% (median 42%), the level of lymphocytes from 12% to 74% (median 41%), the level of monocytes from 2% to 50% (median 14%), and the level of erythrocyte sedimentation rate (ESR) from 4 to 16 mm/h (median 9 mm/h). C-reactive protein (CRP) ranged from 4 to 48 mg/L (median 19 mg/L).

Most biochemical tests were normal, only the level of transaminase was elevated in four patients (19%): alanine aminotransferase (ALT) 100–2,650 IU/L, aspartate aminotransferase (AST) 70–1,800 IU/L. We did not find significant changes in coagulation tests: fibrinogen ranged from 2.3 to 3.9 g/L (median 2.9 g/L); activated partial thromboplastin time (aPTT) from 24 s to 46 s (median 33.7 s); prothrombin time (PT) from 13 s to 17.4 s (median 15.2 s). However, two patients with ALL were diagnosed with venous thrombosis: one patient had catheter-associated thrombosis of vena jugularis sinistra and was treated with enoxaparin for

10 days. Another patient had thrombosis of a small branch of v.tibialis dextra and was treated with enoxaparin for one week and rivaroxaban for three weeks. In both patients, anticoagulants were effective. Chest X-rays, computed tomography (CT)-scans, and ultrasound investigations of lung tissue helped diagnose bilateral pneumonia in one patient.

17 patients (81%) from the cohort stopped chemotherapy between the time of COVID-19 diagnosis and the time of a negative PCR test for SARS-CoV-2. In these cases, chemotherapy was stopped for 5 to 30 days (median 14) before being resumed.

One patient (4.7%) with ALL on maintenance treatment had chemotherapy intensity reduced. Two years after allogeneic bone marrow transplantation (allo-BMT), a patient with AML was withdrawn from the chemotherapy program. One patient with a high-risk ALL had first-line chemotherapy alongside COVID-19, but soon after that became critical and died of sepsis caused by antibiotic-resistant *St. hemolyticus*. One patient with early relapse of AML postponed BMT for three months. She experienced a second relapse seven months after allo-BMT and died 12 months later from disease progression.

Patients with overt symptoms of COVID-19 were treated with: wide-spectrum antibiotics; antifungal drugs; granulocyte-colony stimulating factor (G-CSF), in the case of severe cytopenia; intravenous immunoglobulins; and blood product transfusions. At 24 months, overall survival was 85%, and event-free survival was 82%.

The level of IgG against coronavirus six months after the diagnosis of COVID-19 was tested in four patients; IgG against SARS-CoV-2 was detected in two of them.

Discussion

Our analysis of 21 cases of COVID-19 in pediatric patients with hematological malignancies showed that all patients had asymptomatic, mild, or moderate courses of coronavirus-19 infections. This accords with the data of other researchers [9, 11]. The course of COVID-19 in our patients did not depend on the status of the disease (onset of leukemia or remission status) nor to the type of cancer treatment (low-dose chemotherapy or high-dose intensive chemotherapy). This conclusion is supported in the literature [11].

The majority of our patients were male (66%) and 33.3% had the A(II)Rh(+) blood group. The higher percentage of male patients in our study is comparable to another reported study [10]. The most common symptoms of COVID-19 were fever, cough, gastrointestinal symptoms, and dermatitis. In patients with hematological malignancies tested for COVID-19, we did not find any common changes in blood count due to the myelosuppressive effect of the previous chemotherapy. In patients with oncohematological diseases complicated by COVID-19, it is necessary to be aware of liver toxicity and the risk of venous thrombosis. Thrombotic complications were also reported by Diorio et al. [12].

Most patients from the analyzed cohort had a delay with program chemotherapy of no more than two weeks. This is important for the successful treatment of hematological diseases. One of our patients with relapsed AML, who had a long delay in allo-BMT after COVID-19, experienced a second relapse and died from disease progression. Some researchers have suggested that cancer patients can tolerate chemotherapy, including the induction phase, alongside COVID-19 treatment or chemotherapy doses can be modified [11]. However, it is unclear whether dose modification will have an effect on leukemia cure rates. Our patient with ALL, who had first-line chemotherapy simultaneously with COVID-19, soon died of septicemia.

Several authors have stated that in pediatric cancer patients with severe and critical COVID-19, remdesivir and convalescent plasma might have a potential benefit [3, 6]. However, we did not see severe COVID-19 cases in our patients. Our analysis showed that patients with hematological malignancies need the same approach for COVID-19 treatment as for other infective complications.

One patient from the analyzed cohort was diagnosed with ALL soon after the onset of COVID-19. Exposure to viruses can be a leukemia-inducing event [13]. Can a coronavirus infection cause the development of leukemia? The answer may become evident in future with ongoing epidemiological surveillance and scientific investigations.

Conclusions

This study provides an analysis of COVID-19 in pediatric patients with hematological malignancies treated in the Western Ukrainian Specialized Pediatric Medical Center. Most patients infected with SARS-CoV-2 showed a favorable clinical outcome, with a 24-month overall survival rate of 85% and an event-free survival rate of 82%. The overwhelming majority of patients had an asymptomatic, mild, or moderate course of COVID-19. The course of the coronavirus infection in our patients did not depend on the status of the disease (the onset of leukemia or remission status) or the type of cancer treatment (low intensity program chemotherapy or high-dose intensive chemotherapy). 57% of patients did not require hospitalization for COVID-19 and were treated at home while quarantining.

SARS-CoV-2 in the analyzed cohort of patients with blood cancer increased the risk of liver toxicity and venous thrombosis.

Most patients with oncohematological diseases complicated by COVID-19 needed a delay in chemotherapy of no more than two weeks. Interruption of chemotherapy for a longer period can cause treatment failure.

Our patients with hematological malignancies need the same approach for COVID-19 treatment as for other infective complications.

Further investigations are necessary to determine if the coronavirus can induce leukemia.

Authors' contributions

TO, LG — study design and administrative support. VO, SO, BC, KO — important clinical data. TI, DO — developed first draft of manuscript. SM, BN — assisted in writing and editing manuscript. All authors contributed to data analysis and interpretation, data checking, critical revision, and final approval.

Conflict of interest

None.

Financial support

None.

Ethics

The work described in this article has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; and Uniform Requirements for manuscripts submitted to biomedical journals.

References

1. Lu X, Zhang L, Du H, et al. SARS-CoV-2 infection in children. N Engl J Med. 2020; 382(17): 1663–1665, doi: 10.1056/NEJMc2005073, indexed in Pubmed: 32187458.
2. André N, Rouger-Gaudichon J, Brethon B, et al. COVID-19 in pediatric oncology from French pediatric oncology and hematology centers: high risk of severe forms? Pediatr Blood Cancer. 2020; 67(7): e28392, doi: 10.1002/pbc.28392, indexed in Pubmed: 32383827.
3. Mercolini F, Cesaro S. COVID-19 in children and adolescents: characteristics and specificities in immunocompetent and oncohematological patients. Mediterr J Hematol Infect Dis. 2022; 14(1): e2022009, doi: 10.4084/MJHID.2022.009, indexed in Pubmed: 35070216.
4. Ragab D, Salah Eldin H, Taeimah M, et al. The COVID-19 cytokine storm; what we know so far. Front Immunol. 2020; 11: 1446, doi: 10.3389/fimmu.2020.01446, indexed in Pubmed: 32612617.
5. Cron RQ, Caricchio R, Chatham WW. Calming the cytokine storm in COVID-19. Nature Medicine. 2021; 27(10): 1674–1675, doi: 10.1038/s41591-021-01500-9.
6. Yasuhara J, Watanabe K, Takagi H, et al. COVID-19 and multisystem inflammatory syndrome in children: a systematic review and meta-analysis. Pediatr Pulmonol. 2021; 56(5): 837–848, doi: 10.1002/ppul.25245.
7. Schoot TS, Kerckhoffs APM, Hilbrands LB, et al. Immunosuppressive drugs and COVID-19: a review. Front Pharmacol. 2020; 11: 1333, doi: 10.3389/fphar.2020.01333, indexed in Pubmed: 32982743.
8. Valencia-Sanchez C, Wingerchuk DM. A fine balance: immunosuppression and immunotherapy in a patient with multiple sclerosis and COVID-19. Mult Scler Relat Disord. 2020; 42: 102182, doi: 10.1016/j.msard.2020.102182, indexed in Pubmed: 32416330.
9. Hrusak O, Kalina T, Wolf J, et al. Flash survey on severe acute respiratory syndrome coronavirus-2 infections in paediatric patients on anticancer treatment. Eur J Cancer. 2020; 132: 11–16, doi: 10.1016/j.ejca.2020.03.021, indexed in Pubmed: 32305831.
10. Hammad M, Shalaby L, Sidhom I, et al. Management and outcome of coronavirus disease 2019 (COVID-19) in pediatric cancer patients: a single centre experience from a developing country. Clin Lymphoma Myeloma Leuk. 2021; 21(11): e853–e864, doi: 10.1016/j.clml.2021.07.025, indexed in Pubmed: 34420893.
11. Millen GC, Arnold R, Cazier JB, et al. Severity of COVID-19 in children with cancer: report from the United Kingdom Paediatric Coronavirus Cancer Monitoring Project. Br J Cancer. 2021; 124(4): 754–759, doi: 10.1038/s41416-020-01181-0, indexed in Pubmed: 33299130.
12. Diorio C, McNerney KO, Lambert M, et al. Evidence of thrombotic microangiopathy in children with SARS-CoV-2 across the spectrum of clinical presentations. Blood Adv. 2020; 4(23): 6051–6063, doi: 10.1182/bloodadvances.2020003471, indexed in Pubmed: 33290544.
13. Taub JW, Ge Y, Xavier AC. COVID-19 and childhood acute lymphoblastic leukemia. Pediatr Blood Cancer. 2020; 67(7): e28400, doi: 10.1002/pbc.28400, indexed in Pubmed: 32400927.