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A 10-year-old girl with late Acute Lymphoblastic Leukemia recurrence diagnosed with COVID-19 and treated with remdesivir

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Key words

Acute Lymphoblastic Leukemia, COVID-18, SARS-CoV-2, remdesivir, pediatrics

Abstract

Patients with haemato-oncological diseases are particularly vulnerable to severe infections. Adult patients with blood cancers infected with SARS-CoV-2 had poorer treatment outcomes and higher mortality than patients with COVID-19 without burden. However, in pediatric patients with haemato-oncological diseases the course of COVID-19 is milder than in adults in the same group of patients. In this report, we describe the case of our patient with Acute Lymphoblastic Leukemia (ALL) infected with SARS-CoV-2 and treated with remdesivir. We also review the existing literature of pediatric patients who have been diagnosed with both with haemato-oncological diseases and COVID-19.

Case Report

A nearly 10-year-old girl was admitted to the hospital for a scheduled cycle of consecutive chemotherapies due to the late isolated recurrence of Acute Lymphoblastic Leukemia (ALL) in the bone marrow. On admission, the child's general condition was described as good, with no signs of infection, and the girl did not report any complaints. The screening smears for SARS-CoV-2 taken from the nose of the girl and her mother and analyzed by RT-PCR gave negative results. These results of the laboratory tests made it possible to continue the treatment of the underlying disease. Between the 2nd and the 7th day of hospitalization, the girl received the SCA5 block without complications, but then she developed stomatitis requiring treatment, initially with micafungin and then with amphotericin B. In the following days, bone marrow suppression occurred, and morphology showed pancytopenia with agranulocytosis, which required multiple transfusions of concentrated red blood cells and concentrated platelets. On the 12th day of hospitalization, the girl began to cough. The next day, inflammatory markers increased (CRP to 7.9 mg/dl from 0.7 mg/dl on 08.10., PCT 0.65 ng/ml). Due to the persistent agranulocytosis, after the blood cultures were performed, standard therapy with cefepime was applied. On the 14th day of hospitalization, the patient was positive for *Clostridioides difficile* in stool culture; the metronidazole treatment was applied for ten days. On day 16th, the tests for fungal antigens in the blood (*Candida*, *Aspergillus*, *Cryptococcus neoformans*) were performed, which yielded negative results. On the 17th and 18th day of hospitalization, i.e., on the 5th and 6th day of antibiotic therapy, the girl had an episode of fever followed by a 4-day fever-free period. On the day 21st of the hospital stay, the girl began to fever again, this time up to 39 ° C. After the blood cultures and swabs for alarm pathogens identified *E. coli* ESBL+, the antibiotic therapy was modified to meropenem. In the following days, despite the use of broad-spectrum antibiotic therapy, the fever continued, and the inflammation markers increased. On the 23rd day of hospitalization, the girl showed a decrease in oxygen saturation to 86%, thus requiring passive oxygen therapy. On the same day, to look for the infection source, an ultrasound examination of the abdominal cavity was performed. No significant abnormalities were detected. Also, a CT scan of the chest was performed, in which massive, scattered areas of the ground glass-type were described, merging into parenchymal consolidations with bronchial distribution including all lobes. Treatment with amphotericin B was replaced by the caspofungin and voriconazole due to the suspicion of fungal invasive lung disease. The next smear for SARS-CoV-2 was taken. On

day 25, after receiving a positive SARS-CoV-2 result by RT-PCR test, the girl was transferred to the Isolation Unit for further treatment. In laboratory tests collected on the 26th day of hospitalization, the highest CRP and PCT level was recorded, 17 mg/dl and 35.98 ng/ml, respectively.

The girl was consulted by two specialists in pulmonology and infectious diseases, who concluded that the presented symptoms and the changes described in the chest CT, were with a high probability, the effect of COVID-19. They decided that the compassionate use of remdesivir should be applied. The Local Bioethics Committee was informed about the proposed treatment. Written consent was obtained from the girl's mother to administer the drug off-label. On the hospitalization day 26, remdesivir was introduced at a dose of 5 mg/kg/dose on the first treatment day, and then 2.5 mg/kg/dose for four days. During the treatment with remdesivir, the hepatic and renal parameters did not show any adverse effects. During the Isolation Ward hospitalization, the girl's general condition improved, and the fever subsided. Starting from the 27th day of hospital stay, the parameters of inflammation gradually decreased. From the 28th day onward there was no decrease in oxygen saturation, and the girl did not require passive oxygen therapy. All blood cultures collected at the hospital were negative. On the 38th day of hospitalization, the girl had been discharged home in good general condition with the follow-up recommendations.

Discussion

Severe course of SARS-CoV-2 infection occurs in <3% of children and critical in <1% of cases [1-3]. In these patients, as in the adults, the multi-organ failure with a shock may develop, requiring treatment in an intensive care unit. In children, risk factors are not as well characterized as in adults. The following risk factors were described in a multicentre cohort study conducted in Europe, which enrolled 582 patients <18 years of age with PCR-confirmed SARS-CoV-2 infection: age <1 month, male gender, presence of lower respiratory tract symptoms, and comorbidities [3]. Comorbidities at risk of severe COVID-19 include cancer, developmental delay / genetic defects, immunosuppressive states, obesity, diabetes, congenital heart disease, chronic lung diseases, including asthma, chronic kidney disease, and intussusception [1-3]. Patients with haemato-oncological diseases constitute a group of patients particularly vulnerable

to severe infections. Several studies in adults have shown that patients with blood cancers infected with SARS-CoV-2 had poorer treatment outcomes and higher mortality than patients with COVID-19 without burden [4,5]. In pediatric patients with haemato-oncological diseases, including those treated with chemotherapeutic agents, the course of COVID-19 is milder than in adults in the same group of patients. Similarly to the general population, in pediatric patients group, the course of SARS-CoV-2 infection is usually mild or asymptomatic [6-8]. However, the specialists emphasize the need to exercise particular caution in managing haemato-oncological diseases group of patients due to the existing risk of a severe course of COVID-19 [9].

Remdesivir is an antiviral drug with proven efficacy against SARS-CoV-2 *in vitro* [10]. Recently published results of a large randomized trial have shown that remdesivir is superior to placebo in treating adults with COVID-19 [11]. To date, we have less data on the outcomes of remdesivir treatment in children. For this reason, the case described here may be of special importance. So far, only a few case reports of children with COVID-19 treated with remdesivir have been found in the literature. The youngest was a 19-day-old newborn who received treatment on the 4th day of hospitalization [12]. In all described cases, the children treated with remdesivir achieved clinical improvement, and no serious side effects were reported. A group of specialists led by K. Chiotos published in the Journal of the Pediatric Infectious Diseases Society in September 2020 the guidelines for the treatment of children with COVID-19, approved by this organization. [13]. These guidelines were also important for us when making therapeutic decisions during the treatment of the patient described in this article. We want to notice that the the FDA approved remdesivir for use in adult and pediatric patients 12 years of age and older and weighing at least 40 kilograms and in hospitalized pediatric patients weighing 3.5 kg to less than 40 kg or hospitalized patients younger than 12 years weighing at least 3.5 kg. Our 10-year old patient fulfilled the last criterion: 30,5 kg, 138 cm, BSA 1.09m².

Conclusions

More research is needed to find optimal treatment regimens for children with severe COVID-19, including the groups of patients with high-risk factors for severe COVID-19. Until appropriate therapeutic standards are developed, and an effective vaccine is introduced to the market, preventive actions aimed at reducing the risk of SARS-CoV-2 infection are of the highest priority.

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