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Coronavirus Pandemic

Application of nirmatrelvir/ritonavir for the treatment of severe COVID-19 in a 3-year-old child

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Abstract

Introduction: Nirmatrelvir/ritonavir (Paxlovid) is an effective antiviral drug for treating coronavirus disease 2019 (COVID-19) in adults. However, Paxlovid treatment of children, especially those who are under 12 years and with severe underlying diseases, is rare.

Case report: A three-year-old COVID-19 patient (weighing 14.5 kg) was infected by the Omicron variant (BA.5.2) after undergoing allogeneic hematopoietic stem cell transplantation. The patient had severe bilateral pneumonia along with recurrent fever. The patient was administered 150 mg of nirmatrelvir plus 50 mg of ritonavir twice daily for 5 days, starting 27 days after the initial severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) positive test. Clinical manifestations and chest computed tomography improved considerably after the treatment. The real time reverse transcriptase polymerase chain reaction (RT-PCR) cycle threshold values increased from 23.92 to 38.40 in the case of *ORF 1-ab* gene, and from 22.22 to 36.28 in the case of *N* gene. Only a mild increase in serum urea nitrogen (10.10 mmol/L), alanine transaminase (ALT, 65 IU/L), and aspartate transaminase (AST, 68.5 IU/L) was observed.

Conclusions: Paxlovid can effectively inhibit the replication of SARS-CoV-2 and help in improving the clinical manifestations in pediatric COVID-19 patients. Our study provided novel information on Paxlovid treatment in very young children.

Key words: COVID-19; nirmatrelvir; ritonavir; Paxlovid; children.

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has seriously threatened the lives of the people, and economic and social development across the world since 2019 [1]. Recent guidelines suggested that nirmatrelvir/ritonavir (Paxlovid) might be used for treating mild-to-moderate coronavirus disease 2019 (COVID-19) in children (12 years old or older, and weighing at least 40 kilograms) who are at high risk of progression to a severe condition [2–4]. However, there was no recommendation for children who were below 12 years old, and only a few instances of the treatment of children below 12 years have been reported [5,6], especially with severe underlying diseases. Here, we report the treatment of a child affected by COVID-19, who was diagnosed with acute myeloid leukemia M5 after allo-hematopoietic stem cell transplantation (HSCT).

Case report

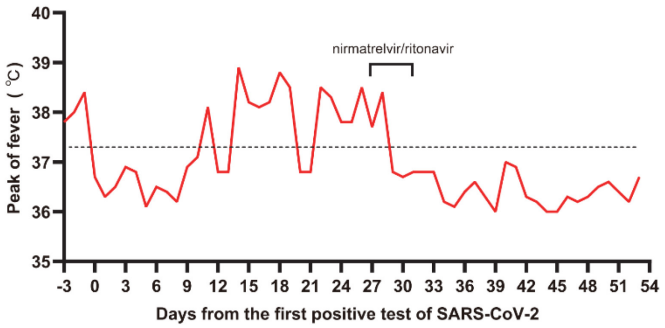
A male patient (1 year and 11 months old) was admitted to Xinqiao Hospital in Chongqing, China, on 18 November 2021. The patient had fever associated with anemia and thrombocytopenia. After bone marrow aspiration and biopsy, the patient was diagnosed with acute myeloid leukemia M5. Combined chemotherapy was administered on 25 November 2021, and the induction regimens consisted of idarubicin (IDA, 15 mg/m^2), cytosine arabinoside (Ara-C, 4 mg/kg), and homoharringtonine (HHT, 0.1 mg/kg). The patient received complete remission on 28 February 2022, and showed negative minimal residual disease on 22 April 2022. A preconditioning regimen consisting of busulfan (BU, 0.8 mg/kg), cyclophosphamide (CTX, 1.8 g/m^2), Arc-a (2 g/m^2), and anti-thymocyte globulin (ATG, 2.5 mg/kg) was administered before transplantation. The patient then received HSCT from his partially HLA-matched (8/12) father (monocytes 14.14 × 10^8/kg, CD34+ cells 15.8 × 10^6/kg) on 29–30 June 2022. Cyclosporine, methotrexate, and mycophenolate mofetil were administered to prevent graft-versus-host disease (GVHD). Neutrophil engraftment was observed on day +10 after transplantation, and platelet engraftment was observed on day +17. The patient was

routinely followed in the clinic. No evidence of transplant-related complications was found.

During the Omicron variant epidemic in Chongqing in December 2022, the patient had a fever on 14 December 2022 after being in contact with his SARS-CoV-2-infected mother. He was not vaccinated because of his underlying disease. The pharyngeal swab of the patient was positive for the SARS-CoV-2 nucleic acid on 17 December 2022 (day 0: the first day of the SARS-CoV-2-positive test). His fever lasted only 2 days without any other symptoms, and he was not administered any antiviral drug. On day 11 (28 December 2022), he was admitted again to our hospital with a 1-day history of medium-grade fever (38.0–38.4 °C), cough, nasal obstruction, rhinorrhea, headache, stomachache, and fatigue. He was 3 years old and weighed 14.5 kg. During admission, his vital signs were normal, and his oxygen saturation was 95% in room air. The SARS-CoV-2 nucleic acid test was still positive. Routine blood examination revealed that the patient had 4.43 × 10^9/L white blood cells (WBCs), 50.6% neutrophils, 34% lymphocytes, 87 g/L hemoglobin (HB), 248 × 10^9/L platelets (PLT), 19.8 mg/L C-reactive protein (CRP), and 0.19 ng/mL procalcitonin (PCT). Chest X-ray examinations showed mildly patchy opacities. He was diagnosed with pneumonia, and SARS-CoV-2 was suspected as one of the pathogens, but we could not exclude bacterial infections because of his long-term use of anti-rejection drugs. Therefore, piperacillin sodium and tazobactam sodium were administered for antibacterial therapy. On day 17 (3 January 2023), he still had a fever and developed neutropenia (WBC 1.65 × 10^9/L, neutrophils 0.91 × 10^9/L, lymphocytes 0.42 × 10^9/L, HB 73 g/L, PLT 139 × 10^9/L, and CRP 18.9 mg/L). The chest computed tomography (CT) examination showed significant bilateral lower lobe pneumonia. The antibiotics were changed to meropenem. Intravenous immunoglobulin (IVIG,10 g, 0.7 g/kg) and red blood cell infusion were administered as supportive treatment.

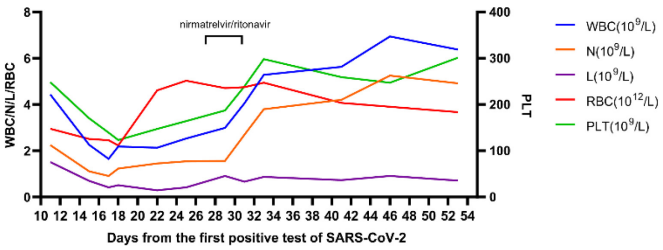
However, the fever and cough persisted. On day 26 (12 January 2023), the patient developed hypoxemia (oxygen saturation below 90% in room air). The reports of blood tests still showed low WBC count (2.53 × 10^9/L), neutrophils 1.53 × 10^9/L, and CRP below 5.0 mg/L). The chest CT showed more severe pneumonia than before. The bone marrow examination was normal, and the short tandem repeat test showed that the donor chimerism of whole blood cells was 100%, suggesting stable mixed chimerism without graft failure and relapse. Sputum culture and blood culture showed negative results. The results of next-generation sequencing (NGS) of the throat swab indicated SARS-CoV-2 BA.5.2 infection with 34,064 reads, while no other pathogens were found. We re-tested SARS-CoV-2 nucleic acid and found positive results. The RT-PCR cycle threshold (Ct) values of the *ORF 1-ab* and *N* gene fragments were 23.92 and 22.22, respectively. Therefore, an off-label 5-day-course treatment with 150 mg of nirmatrelvir plus 50 mg of ritonavir administered twice daily was started on day 27 (13 January 2023) after taking consent from the legal guardians and approval from a group of COVID-19 experts and the ethical committee. The administration of meropenem was stopped. On day 29 (15 January 2023), the fever disappeared (Figure 1), and the WBC count started increasing (Figure 2). After the five-day full course of Paxlovid therapy, the patient had complete remission of clinical symptoms. The Ct values increased to 38.40 (*ORF 1-ab* gene) and 36.28 (*N* gene) (Figure 3). The reports of routine blood tests were normal. The chest CT showed that bilateral pneumonia decreased significantly (Figure 4). However, two weeks after Paxlovid treatment, the Ct values again decreased to 26.30 (*ORF 1-ab* gene) and 26.33 (*N* gene), respectively. The clinical manifestations, blood routine,

Figure 1. Trend of fever over time. Nirmatrelvir/ritonavir was administered on day 27 to day 31.



SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

Figure 2. Trend of hematologic parameters over times. Nirmatrelvir/ritonavir was administered from day 27 to day 31.



L: lymphocytes; N: neutrophils; PLT: platelets; RBC: red blood cells; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; WBC: white blood cells.

and chest CT did not show any rebound within the next month.

The patient tolerated Paxlovid without severe problems. However, a mild increase in serum urea nitrogen (10.10 mmol/L), alanine transaminase (ALT, 65 U/L), and aspartate transaminase (AST, 68.5 U/L) was observed on the third day of Paxlovid therapy. One week after stopping Paxlovid treatment, the serum levels of ALT and AST returned to normal.

Discussion

Paxlovid, a combination of ritonavir and nirmatrelvir, was authorized for emergency use by the US Food and Drug Administration (FDA) in December 2021 [7]. Nirmatrelvir is an orally active 3Cl protease inhibitor that can inhibit the main SARS-CoV-2 protease and prevent the virus from replicating [8]. Ritonavir can inhibit the metabolism of nirmatrelvir by cytochrome P450 3A4 isoenzyme (CYP3A4), thus increasing the plasma concentration of nirmatrelvir, but it does not directly affect SARS-CoV-2 [8]. A meta-analysis that included 23 studies involving 314,353 patients (mostly adults) showed that treatment with Paxlovid was effective for patients with COVID-19, and it reduced the mortality rate, hospitalization rate, and polymerase chain reaction (PCR) negative conversion time. No significant difference in rebound and adverse events was recorded in the Paxlovid group relative to the control group [9–11]. A large-scale

Figure 3. Trend of the cycle threshold (Ct) values of ORF 1-ab and N genes over time. Nirmatrelvir/ritonavir was administered on day 27 to day 31.

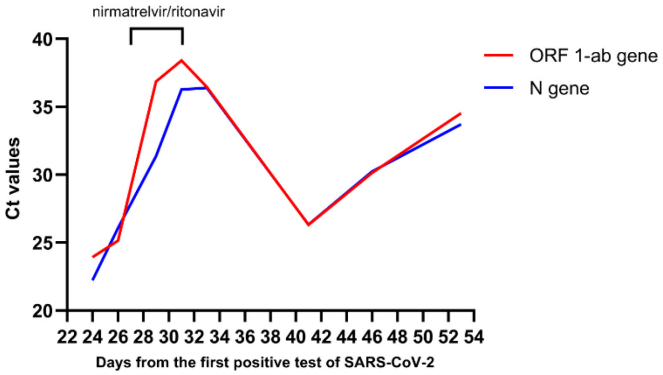
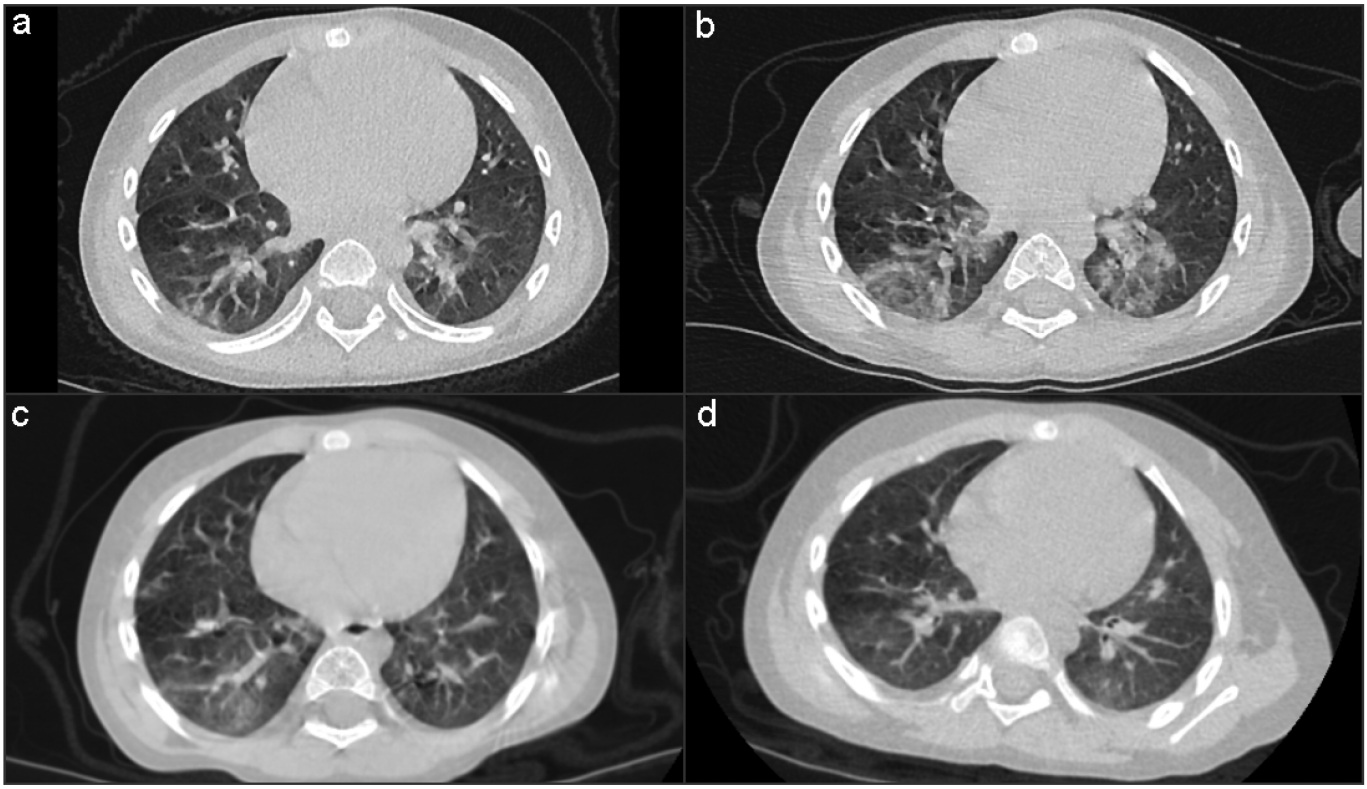


Figure 4. Axial non-enhanced computed tomography (CT) of the three-year-old case of coronavirus disease 2019 (COVID-19).



a. Taken on day 17 (3 January 2023), before treatment with Paxlovid. Fairly modest patchy ground-glass opacities in the lung, especially in the bilateral lower lobe can be observed; **b.** Taken on day 26 (12 January 2023) before treatment with Paxlovid. More severe pneumonia than before, especially in the bilateral lower lobe, can be observed; **c.** Taken on day 33 (19 January 2023), two days after the treatment with Paxlovid. Pneumonia in the bilateral lower lobe was significantly decreased than before; **d.** Taken on day 46 (1 February 2023), two weeks after the Paxlovid course. The image shows that the pneumonia was almost absorbed.

clinical trial of Paxlovid has rarely been performed with children, especially younger children. Three case reports [5,6,12] containing 9 cases (5–17 years old, 15–63 kg) showed that administration of Paxlovid within 5 days of the onset of symptoms provided complete relief and eradicated the SARS-CoV-2 infection.

In our case, a 3-year-old boy associated with acute leukemia after allo-HSCT was diagnosed with severe COVID-19. We used Paxlovid off-label because of the following reasons. First, the diagnosis of COVID-19 was confirmed, and the patient had persistent fever, which ruled out the possibility of infection by other pathogens, drug-related fever, graft failure, and leukemia relapse. Recurrent IVIG and prednisone therapy did not affect the fever. Second, the patient had severe underlying diseases and received allo-HSCT for several months. Long-term immunosuppressive therapy was also administered to prevent GVHD. Third, he had persistently low levels of neutrophils and lymphocytes after the SARS-CoV-2 infection. In previous studies, cases of neutropenia and immunodeficiency were significantly associated with high disease severity and COVID-19-related mortality in patients after allo-HSCT [13,14]. Fourth, the initial Ct values and NGS results suggested that there was a persistent high viral load. Fifth, dynamic examinations of the chest CT showed aggravating pneumonia. Additionally, the patient was not vaccinated. In consideration of so many life-threatening factors, Paxlovid was administered on day 27 after the initial SARS-CoV-2 infection when we received approval from the ethical committee and his legal guardians. The dose of Paxlovid was decided based on the dose used in the EPIC-PEDS trial and some case reports [5,6,12]. The condition of the patient and the Ct values improved significantly after the 5-day course of Paxlovid. No relapse of symptoms occurred, and routine blood examinations and chest CT in the following month showed that the patient was stable. Additionally, no significant adverse effect was reported.

However, the Ct values decreased again 2 weeks after Paxlovid therapy. This phenomenon was also reported in other studies [5,12]. This pattern indicated persistent low viremia of SARS-CoV-2 in the patient. Some retrospective studies reported that the median time of SARS-CoV-2 clearance is 20 to 27 days in pediatric patients after allo-HSCT, and it might even last for several months for patients with immunodeficiency [5,15–17]. However, the significant improvements in the clinical manifestations and chest CT indicated that Paxlovid can effectively inhibit the replication of SARS-CoV-2. The time of complete clearance of SARS-CoV-2 is not known due to differences in the immune status of different parts of the body. Therefore, in clinical practice, complete clearance of SARS-CoV-2 cannot be considered a major indicator to evaluate the effect of Paxlovid.

Our study was slightly different from previous studies on pediatric COVID-19 cases. First, the patient in this study was younger than in previous studies, and had the lowest weight among patients who had been administered Paxlovid. Our results increased our confidence in the effects and safety of Paxlovid in treating young children as we gained some experience in administering Paxlovid to very young children. Second, our patient was a severe case of COVID-19, and he received Paxlovid treatment even after 5 days of symptom onset. This treatment regimen did not meet the recommendations of the common guidelines, which suggest Paxlovid can be only used in mild-to-moderate COVID-19 patients (≥ 12 years old, weight ≥ 40 kg) within 5 days after symptom onset. However, significant beneficial effects of Paxlovid were observed in this case. Our findings suggest that there might be a longer window for using Paxlovid in immunodeficient COVID-19 patients. Additionally, patients with severe COVID-19 might also be allowed Paxlovid treatment, as they might benefit from it. Patients with COVID-19 should be evaluated individually, and the benefits and risks of using Paxlovid should be determined for each patient.

Conclusions

We present a case report in which Paxlovid was used for treating COVID-19 in a child with leukemia after allo-HSCT. We found that Paxlovid can effectively inhibit the replication of SARS-CoV-2 and can improve clinical manifestations in pediatric COVID-19 patients. Paxlovid does not cause any significant adverse reaction. Our study provided novel information on Paxlovid treatment in very young children.

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