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Treatment with convalescent plasma for critically ill patients with SARS-CoV-2 infection

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Abstract

As of March 24, 2020, novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been responsible for 379,661 infection cases with 16,428 deaths globally and the number is still increasing rapidly. Herein, we presented four critically ill patients with SARS-CoV-2 infection who received supportive care and convalescent plasma. Although all the four patients (including a pregnant woman) recovered from SARS-CoV-2 infection eventually, randomized trials are needed to eliminate the effect of other treatments and investigate the safety and efficacy of convalescent plasma therapy.

Keywords: SARS-CoV-2; Convalescent plasma; Critically illness

Introduction

Since late December 2019, an outbreak of novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection first appeared in Wuhan, China (1), and rapidly spread to 171 countries. As of March 24, 2020, the virus has been responsible for 379,661 confirmed cases and 16,428 deaths worldwide. To date, no specific treatment was recommended for SARS-CoV-2 infection except for meticulous supportive care (2). Numerous therapeutics were explored or developed during the outbreak. A recent trial showed lopinavir-ritonavir has no treatment benefit for severe illness caused by SARS-CoV-2 (3). Immunotherapy with virus-specific antibodies in convalescent plasma had been used as a last resort to improve survival rate of patients with serious infectious diseases, such as SARS, middle east respiratory syndrome coronavirus, Ebola virus disease, pandemic influenza A, and avian-origin influenza A (4). Previous reports showed treatment with convalescent plasma collated from recovered patients could reduce the hospital stay and mortality of patients (5). However, the efficacy of convalescent plasma in critically ill patients with SARS-CoV-2 infection remains unclear. Herein, we reported the disease course on four critically ill SARS-CoV-2-infected patients treated with supportive care and convalescent plasma.

Case reports

Figure 1 showed the clinical course of the four critically ill patients infected with SARS-CoV-2. Our first case was a 69-year-old female with a history of hypertension who

presented with fever for two days and clear sputum for four days. On January 30, the patient was admitted to Dongguan Ninth People's Hospital because of positive reverse transcriptase polymerase chain reaction (RT-PCR) test of throat swab by Dongguan Center for Disease Control (CDC). A chest CT revealed bilateral ground-glass opacities primarily distributed along the pleura. Treatment with arbidol (200 mg three times daily), lopinavir-ritonavir (400 mg twice daily), interferon alpha inhalation (50 μg twice daily), and other supportive therapies was started. At 4 p.m. on February 4, the patient's oxygen pressure (pO_2) decreased to 56.5 mmHg with OI of 94 mmHg. Significantly increased consolidation was observed in the right lung. The patient was transferred to the intensive care unit (ICU) of Dongguan People's Hospital (a designated center for critically illness treatment) on February 5 and received invasive mechanical ventilation. Apart from antiviral drugs (lopinavir-ritonavir, oseltamivir, and interferon alpha), human albumin, zadaxin and immunoglobulin, antibacterial and antifungal drugs were administrated because of co-infection with bacteria and aspergillus. At 6:30 p.m. on February 11, the patient's pO_2 was 58 mmHg. She experienced septic shock with blood pressure of 89/44mmHg five hours later. Hypohemoglobin (92 g/L) and bloody sputum under bronchoscopy suggested pneumorrhagia. A bedside chest radiography showed obvious progression of disease. Although the patient was successfully rescued, follow-up chest radiographs showed continuous progression of pneumonia. A total of 900 ml O-compatible convalescent plasma were transfused to the patient in three batches; the first batch was given at 8 a.m. on February 17 (200 ml), the second one was at 8 a.m. on February 27 (400 ml), and the last one was at 8 a.m. on February 28 (300 ml). The virus load of the patient on February 18 was 55×10^5 copies per milliliter, which significantly decreased to 3.9×10^4 copies per milliliter on February 28, and further decreased to 180 copies per milliliter on March 5. The patient was extubated and non-invasion ventilation was given on March 3. Chest CT obtained on February 27, March 6, and March 15 showed persistent absorption of consolidation. The results of two repeat RT-PCR tests of oropharyngeal swabs (with at least one day interval) performed on March 9 and 11 were negative. The patient was discharged on March 13.

Our second case was a 55-year-old male with a history of chronic obstructive pulmonary disease who was admitted to a fever clinic of Xiangtan Central Hospital on February 5, 2020. He had nausea, poor appetite, and a cough with clear sputum for four days. The results of RT-PCR assay of throat swab was positive for SARS-CoV-2 infection. A chest CT obtained on February 6 revealed interlobular septal thickening with honeycombing change in the right upper lung. The patient started to receive antiviral treatment, including arbidol (200 mg three times daily), lopinavir-ritonavir (500 mg twice daily), and interferon alfa-2b (5 million units twice daily). After two days, he complaint of shortness of breath and the pO_2 decreased to 50 mmHg with oxygenation index (OI: pO_2/FiO_2) of 135 mmHg. The patient was thus diagnosed with acute respiratory distress syndrome and began to receive noninvasive mechanical ventilation and oxygen therapy through high-flow nasal cannula alternately. However, the conditions of the patient continued to deteriorate despite treatment with pulsed methylprednisolone. His pO_2 oscillated between 46 and 83 mmHg and the symptoms were not improved. Follow-up chest CT obtained on February 9 to 16 showed interstitial pneumonia extend to both lungs. At 3 p.m. on February 16, 200 ml convalescent plasma obtained from a patient recovered from SARS-CoV-2 infection in January, 2020 was transfused to the patient. No adverse reactions were observed. One day later, his pO_2 increased to 97 mmHg with OI of 198 mmHg. All drugs were discontinued except for methylprednisolone. Chest images obtained on February 17 to 21 showed obvious absorption of interstitial pneumonia. Three repetitive RT-PCR test results were negative from February 20 to 22. The patient recovered and was discharged on February 23. He was asked to continue the quarantine at home for 14 days and receive home oxygen therapy.

Our third case was a 73-year-old male who was admitted to Dongguan Ninth People's Hospital on February 2 because of self-reported dry cough for 4 days. He had a history of hypertension and chronic renal failure. On February 3, this patient was confirmed as being infected with SARS-CoV-2 by a virus RNA detection kit. At 23: 30, the patient developed acute respiratory failure with pO_2 of 53 mmHg and OI of 124 mmHg,

high-flow oxygen through face mask was given. He was then transferred to the isolation wards of ICU of Dongguan People's Hospital for further treatment. A chest radiograph showed bilateral infiltrative shadows. The viral load of the patient was as high as 85 × 10^5 copies per milliliter. The patient was treated with arbidol (200 mg three times daily), lopinavir-ritonavir (400 mg twice daily), oseltamivir (75 mg twice daily), and ribavirin and interferon alpha-2b (5 million units twice daily). On February 5, the patient was given tracheal intubation because of dyspnea and consistent decrease of oxygen saturation. On February 11, continuous renal replacement therapy (CRRT) started to given to the patient. Laboratory tests obtained on February 14 showed significantly increased white cells of 33.93 × 10^9/L and neutrophils of 31.08 × 10^9/L. He was diagnosed with multiple organ failure by clinical examination. On February 15, the patient developed septic shock and his blood pressure decreased to 90/68 mmHg with heart rate of 149 beat/min and respiratory rate of 30 breaths/min. A chest radiography showed bilateral "white lung". At 12:55 p.m. on February 15, the patient started to receive veno-venous extracorporeal membrane oxygenation (V-V ECMO), while the oxygenation index was unstable and the symptoms were not improved. High-throughput DNA sequencing of sputum suggested aspergillus infection. The patient was therefore treated with caspofungin and voriconazole. Eight transfusions of B-compatible convalescent plasma (2400 ml) were given to the patient from February 16 to March 13. On February 21, the patient was confirmed with active pneumorrhagia, cystorrhagia and gastrointestinal bleeding. Antibody testing on February 27 indicated positive anti-SARS-CoV-2 IgG. The viral load was reduced (detailed values were not available). Follow-up chest x-rays showed absorbed infiltrative lesions but pneumothorax. Two repeat RT-PCR test of sputum in deep lung on March 16 and 17 (with at least one day interval) showed negative and the serum IgM level decreased to normal range. On March 22, the patient was transferred to unfenced ICU for further treatment of underlying diseases and multiple organ failure.

Our fourth case was a 31-year-old pregnant woman (35 weeks plus 2 days) who was admitted to Xiaolan People's Hospital of Zhongshan on February 1 because of

pharyngalgia for 4 days and fever (39.3□) and difficulty breathing for half-day. The patient was confirmed as being infected with SARS-CoV-2 by Zhongshan CDC. A chest CT showed opacities in the lower lobe of the left lung. After admission, the patient developed severe acute respiratory distress syndrome, multiple organ dysfunction syndrome, and septic shock. Invasive ventilation and caesarean section were therefore given to the patient. Unfortunately, the newborn died of endouterine asphyxia. After the conditions turned stable, she was transferred to the Second People's Hospital of Zhongshan (a designated hospital for SARS-CoV-2 treatment) at 1:04 a.m. on February 2. Amounts of frothy sputum was observed under bronchofiberscope. Cardiac ultrasound suggested left ventricular enlargement with decreased systolic function. The patient received invasive ventilation and CRRT. Treatment with lopinavir-ritonavir (400 mg twice daily) and ribavirin (500 mg every 12 hours) was started on February 2. Gram-positive bacteria were detected by blood culture and imipenem and vancomycin were given to this patient. A chest radiograph showed increased consolidation and extended opacities. Oxygen saturation oscillated between 85% and 92% with OI of between 60 mmHg and 75 mmHg. At 12 a.m. on February 6, the patient started to receive V-V ECMO (flow rate: 3L/h). Her OI was significantly improved (with a maximum of 200 mmHg). Follow-up chest radiographs showed partial absorption of opacities. Left ventricular systolic function returned to normal. At 11:30 on February 19, a 300 ml transfusion of convalescent plasma were given to this patient. On February 27, CRRT and ECMO were removed. On March 11, trachea cannula was removed and nasal oxygen was given to the patient. On March 6, 8, and 11, anti-SARS-CoV-2 IgM changed from positive to weakly positive to negative, while anti-SARS-CoV-2 IgG was persistently positive. Follow-up chest CT showed near-complete absorption of opacities. The results of two continual RT-PCR tests of broncholveolr lvge fluid on March 11 and 14 were both negative. The patient recovered from SARS-CoV-2 infection and was discharged on March 17.

Discussion

A recent retrospective review of 72,314 SARS-CoV-2-infected cases by the China CDC

showed that 5% of the cases were critically illness characterized by respiratory failure, septic shock, and/or multiple organ dysfunction or failure. Around 48% of SARS-CoV-2-infected patients had comorbid conditions, commonly cardiovascular diseases and diabetes (9). Elderly people with underlying diseases were more likely to have higher Sequential Organ Failure Assessment score and higher risk of death. The treatment of SARS-CoV-2 infection faces compelling challenges. To date, no therapeutics have yet been proven effective for the treatment of critically illness except for supportive care, including treatment with antiviral drugs, corticosteroids, immunoglobulins, and noninvasive or invasive mechanical ventilation. Most critically ill patients infected with SARS-CoV-2 had elevated levels of infection-related biomarkers and inflammatory cytokines, indicating potential bacterial co-infection caused by dysregulated immune system (10). Antibacterial drugs are therefore given to these patients. Management of critical SARS-CoV-2 infection is not different from management of most viral pneumonia causing respiratory failure. The principal feature of patients with critical illness is the development of ARDS. ECMO is recommended by WHO interim guidelines to support eligible patients with ARDS, while the use of which is restricted to specialised centres globally and technology challenges (11). In this study, two patients were treated with ECMO, but the efficacy was mixed. Apart from ARDS, other life-threatening conditions including septic shock and multiple organ dysfunction or failure may occur in a substantial proportion of patients with SARS-CoV-2-related critically illness, the management of which was according to current evidence based guidelines (12). In China, if the current therapeutic strategies are not satisfactory for critically ill patients, physicians might turn to convalescent plasma transfusion based on the Pneumonitis Diagnosis and Treatment Program for SARS-CoV-2 infection (Trial Version 7). Convalescent plasma had been used as a last resort to improve survival rate of patients with SARS-infection. Previous evidences proved that convalescent plasma treatment can significant reduce the relative risk of mortality of patients (13), which might because that antibodies from convalescent plasma might suppress viraemia. The level of SARS-CoV-2 neutralizing antibodies in donor plasma could be important for the

effectiveness of intervention. However, the level of neutralizing antibodies in donor plasma before transfusion cannot be determined. In this study, three patients were tested either virus load or antibodies IgM and IgG. In the first case, SARS-CoV-2 virus load after convalescent plasma transfusion significantly dropped (from 55×10^5 to 3.9×10^4 to 180 copies per milliliter). Among the four patients, the time from the transfusion to negative RT-PCR test results ranged from 3 to 22 days. The third and fourth cases produced anti-SARS-CoV-2 IgG approximately 14 days after convalescent plasma transfusion. Patients who survived critically ill diseases might mount higher antibody responses, which can persist for longer periods as compared with those with non-severe disease (14). The antibody levels, however, were confounded by other treatments, such as antiviral drugs, steroids and intravenous immunoglobulin (15). A recent animal model indicated that antibodies produced from SARS-CoV-2 infection could protect from subsequent exposures (16).

Conclusions

Our results indicated convalescent plasma might be a potential therapy for critically ill patients infected with SARS-CoV-2. We observed no serious adverse reactions associated with the transfusion of convalescent plasma. However, the relative contributions of supportive care, investigational therapies, and patient's immune-response on survival could not be determined. Whether convalescent plasma and/or supportive care provide any clinical benefit is unknown. The safety and efficacy of convalescent plasma transfusion in SARS-CoV-2-infected patients should be studied within the context of a well-designed clinical trial.

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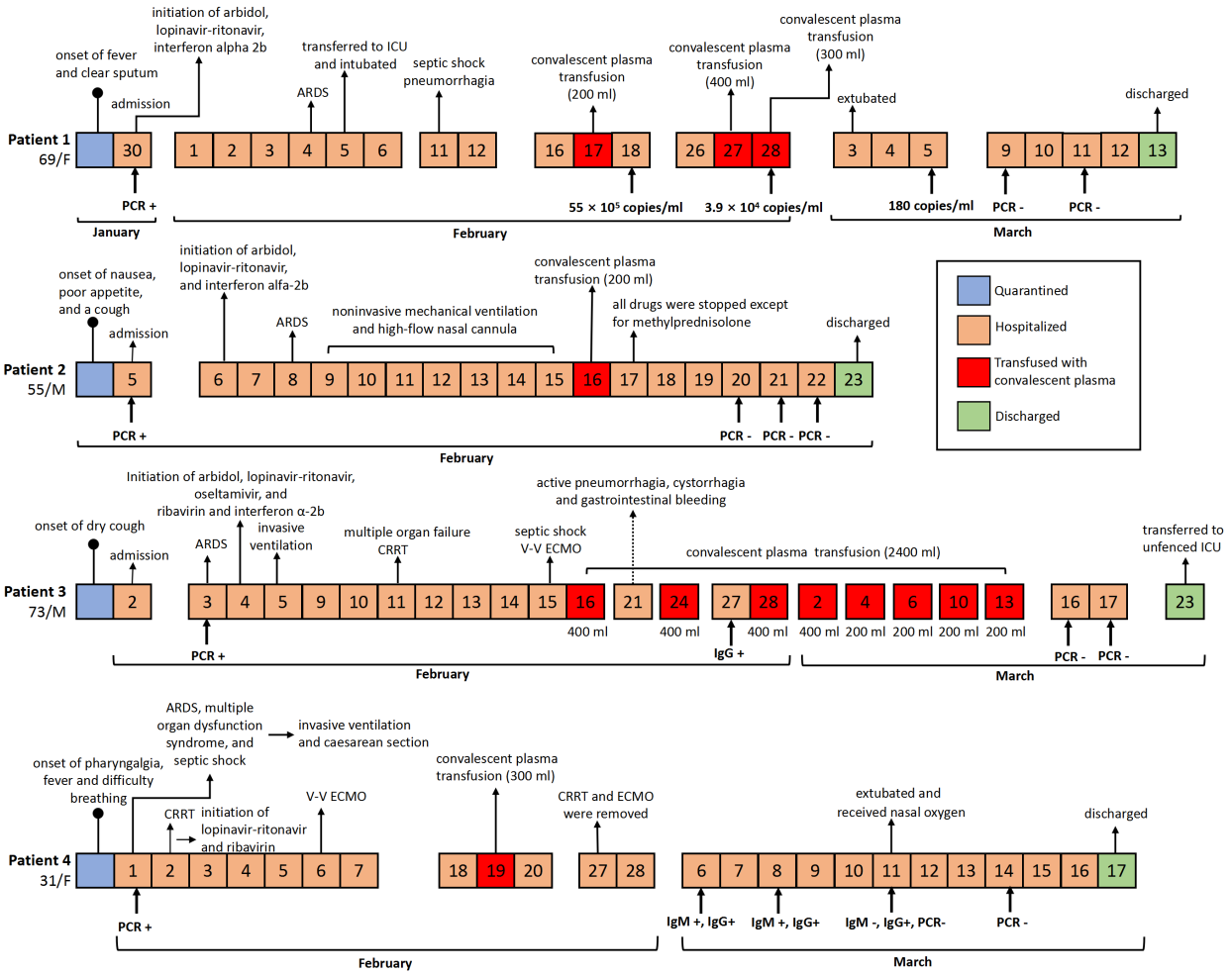
Figure legend

Figure 1: Timeline of symptom onset, RT-PCR testing, antiviral therapies, severe complications, convalescent plasma transfusion, levels of virus load and antibodies after transfusion, and outcomes of the four critically ill patients with SARS-CoV-2 infection. Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RT-PCR, reverse transcriptase polymerase chain reaction; CRRT, continuous renal replacement therapy; V-V ECMO, veno-venous extracorporeal membrane oxygenation; ICU, intensive care unit; ARDS, Acute Respiratory Distress Syndrome.


Patient 1
69/F
onset of fever and clear sputum
admission
initiation of arbidol, lopinavir-ritonavir, interferon alpha 2b
ARDS
transferred to ICU and intubated
septic shock pneumorrhagia
convalescent plasma transfusion (200 ml)
convalescent plasma transfusion (400 ml)
convalescent plasma transfusion (300 ml)
extubated
discharged
PCR +
55 × 10⁵ copies/ml
3.9 × 10⁴ copies/ml
180 copies/ml
PCR -
PCR -
January
February
March
Patient 2
55/M
onset of nausea, poor appetite, and a cough
admission
initiation of arbidol, lopinavir-ritonavir, and interferon alfa-2b
ARDS
noninvasive mechanical ventilation and high-flow nasal cannula
convalescent plasma transfusion (200 ml)
all drugs were stopped except for methylprednisolone
discharged
PCR +
PCR -
PCR -
PCR -
February
Quarantined
Hospitalized
Transfused with convalescent plasma
Discharged
Patient 3
73/M
onset of dry cough
admission
Initiation of arbidol, lopinavir-ritonavir, oseltamivir, and ribavirin and interferon α-2b
ARDS
invasive ventilation
multiple organ failure
CRRT
septic shock
V-V ECMO
active pneumorrhagia, cystorrhagia and gastrointestinal bleeding
convalescent plasma transfusion (2400 ml)
transferred to unfenced ICU
400 ml
400 ml
400 ml
400 ml
200 ml
200 ml
200 ml
200 ml
PCR +
IgG +
PCR -
PCR -
February
March
Patient 4
31/F
onset of pharyngalgia, fever and difficulty breathing
ARDS, multiple organ dysfunction syndrome, and septic shock
invasive ventilation and caesarean section
CRRT
initiation of lopinavir-ritonavir and ribavirin
V-V ECMO
convalescent plasma transfusion (300 ml)
CRRT and ECMO were removed
extubated and received nasal oxygen
discharged
PCR +
IgM +, IgG+
IgM +, IgG+
IgM -, IgG+, PCR-
PCR -
February
March