Convalescent-anti-sars-cov-2-plasma/tisagenlecleucel

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Various toxicities: 2 case reports

A case series described two patients, of whom, a 16-year-old boy developed cytokine release syndrome (CRS), COVID-19 and interstitial pneumonitis during treatment with tisagenlecleucel and type 1 hypersensitivity reaction during compassionate use of convalescent-anti-SARS-CoV-2-plasma, while a 24-year-old man developed CRS, immune effector cell associated neurotoxicity syndrome (ICANS) and atrial fibrillation during treatment with tisagenlecleucel [*dosages not stated*].

Case 1: The 16-year-old boy, with a history of refractory B-cell acute lymphoblastic leukaemia (B-ALL) received CD-19 CAR-T therapy with tisagenlecleucel infusion (day 0). Prior to the CAR-T therapy, nasopharyngeal swab for SARS-CoV-2 were negative. However, his post-CAR-T course was complicated by grade 3 CRS, for which he received tocilizumab once. After 2 weeks of CAR-T infusion, he was discharged from the hospital. Subsequently, he achieved complete ALL remission. On day +70 post-CAR-T therapy, he developed intermittent headaches for 2 days, which resolved with paracetamol [acetaminophen] at home. After 1 week (day +77), he reported nasal congestion, persistent intermittent headaches and generalised fatigue for few days. At that time, he denied exposure to SARS-CoV-2 or fever. His physical examination was at baseline and blood test results revealed transaminitis. After 1 week (day +84), he developed mild cough with no associated fever or dyspnoea. Subsequent respiratory PCR and nasopharyngeal swab for SARS-CoV-2 returned negative, while a chest x-ray showed sub segmental atelectasis. After few days, he reported tactile fever and malaise. In clinic, he was afebrile and well-appearing and had an improvement of transaminitis. On day +95, he was hospitalised due to a productive cough accompanied by dyspnoea, headache, dizziness and fever. A repeat respiratory PCR and nasopharyngeal testing for SARS-CoV-2 returned negative, while a chest-CT showed bilateral multifocal pneumonia and suggestion of a reverse halo sign. Ensuing SARS-CoV-2 IgG and IgM antibodies were found to be negative. At that time, he exhibited B cell aplasia, consistent with CAR therapy response. Subsequently, he underwent bronchoalveolar lavage (BAL) and received unspecified broad spectrum empiric antimicrobial therapy due to his immune compromised status and IV immune-globulin [immunoglobulin] (IVIG) for hypogammaglobulinaemia. From the BAL, the SARS-CoV-2 test result was not obtained. In the meantime, he required oxygen supplementation with high flow nasal cannula and bilevel positive airway pressure for progressive dyspnoea/hypoxaemia. On day +117, a repeat chest-CT showed significant improvement of bilateral lung opacities; however, new opacities were noted within the left upper lobe. Lung biopsy showed interstitial pneumonitis. Subsequently, he had clinical improvement and was afebrile, with no oxygen requirement for 8 days prior to discharge. Eventually, he was discharged. On day +150, he was re-admitted for evaluation of fever and persistent cough. Subsequent chest-CT scan showed interval worsening of bilateral multifocal pneumonia. Sputum culture returned positive for haemophilus species. Respiratory PCR and SARS-CoV-2 nasopharyngeal test were again returned negative. However, a repeat BAL was positive for SARS-CoV-2 on day +152 (COVID-19). Therefore, he started receiving convalescent-anti-SARS-CoV-2-plasma (convalescent plasma) infusion on compassionate basis. However, during his first infusion on day +154, he developed a possible type I hypersensitivity reaction to convalescent-anti-SARS-CoV-2-plasma. Therefore, convalescent-anti-SARS-CoV-2-plasma was discontinued. As he exhibited poor humoral immunity with B-cell aplasia, he received five doses of remdesivir from day +154 to day +158 without adverse events. He also received prophylactic unspecified low molecular weight heparin from day +154 to day +160. On day +160, he was discharged in good clinical condition, and his recent chest x-ray was found to be normal. All the clinical symptoms resolved. However, he developed CD19+ ALL relapse on day +179.

Case 2: The 24-year-old man, with a history of relapsed B-ALL, received CD19 CAR-T therapy with tisagenlecleucel infusion (day 0). However, the treatment course was complicated by grade 3 CRS and grade 2 ICANS with temporally associated atrial fibrillation. He received treatment with tocilizumab and dexamethasone, and subsequently all symptoms resolved. Later, he achieved clinical remission with salvage therapy. Subsequently, he underwent related haploidentical peripheral blood stem cell transplant (139 days post-CAR-T therapy). Post-transplant, he was treated with cyclophosphamide followed by mycophenolate-mofetil and tacrolimus for graft-versus host disease prophylaxis. His transplant course was complicated by hepatic sinusoidal obstructive syndrome (treated with defibrotide) with multi-organ dysfunction. Later he was readmitted due to human herpes virus-6 (HHV6) infection [*aetiology not stated*], which was treated with foscarnet. Later, he developed acute respiratory distress with bilateral pneumonia and pleural effusions (On day +67) requiring mechanical ventilation; fluid overload and non-oliguric acute kidney injury requiring renal replacement therapy; cardiac dysfunction and pericardial effusion (on day +102) treated with methylprednisolone; and capillary hemangiomatosis/organizing pneumonia (detected on lung biopsy performed on day +106). Therefore, he was treated with milrinone. A subsequent review of his clinical history revealed multi-system inflammation affecting his brain, kidney, heart, and lungs with increased inflammatory markers. A diagnosis of multisystem inflammatory syndrome-Adult (MIS-A) was made on day +113. Therefore, he was treated with immune-globulin (IVIG) followed by tocilizumab with gradual improvement of his multi-organ dysfunction. He also received prophylactic dose of unspecified low molecular weight heparin. After improvement, he was weaned to nasal cannula with no cardiac and renal support.

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