Pumpless extracorporeal interventional lung assist for bronchiolitis obliterans after allogenic peripheral blood stem cell transplantation for acute lymphocytic leukemia

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Bronchiolitis obliterans (BO), which is associated with graft-versus-host disease after allogenic hematopoietic stem cell transplantation, is a major obstacle to survival after bone marrow transplantation due to its gradual progress, eventually leading to respiratory failure. Pumpless extracorporeal interventional lung assist (iLA) is effective in treatment of reversible hypercapnic respiratory failure. In this paper, we present a 23-year-old female patient who underwent allogeneic peripheral blood stem cell transplantation (PBSCT) for acute lymphocytic leukemia. After 6 months, she complained of shortness of breath and was diagnosed with BO. Five months later, she developed an upper respiratory tract infection that worsened her BO and caused life-threatening hypercapnia. Since mechanical ventilation failed to eliminate CO₂ effectively, iLA was applied as rescue therapy. Her hypercapnia and respiratory acidosis showed significant improvement within a few hours, and she was successfully weaned off iLA after 12 days. This is the first case report of iLA application for temporarily aggravated hypercapnia of PBSCT-associated BO followed by successful weaning. This rescue therapy should be considered in ventilator-refractory reversible hypercapnia in BO patients.

Keywords: Bronchiolitis obliterans; Graft vs host disease; Pumpless extracorporeal interventional lung assist; Hypercapnia

INTRODUCTION

Bronchiolitis obliterans (BO) is characterized by the progression of fixed small-airway obstruction and is associated with chronic graft-versus-host disease (GVHD) after allogeneic hematopoietic stem cell transplantation (HSCT) [1]. Biopsy specimens usually show bronchiolitis involving the small airways and fibrous obliteration of the lumens of the respiratory bronchioles. The overall prevalence of BO is 5.5%, while prevalence in patients who survived at least 1 year after HSCT is 10% and 16% in all patients with chronic GVHD. The prognosis of BO is poor, with an overall survival rate of 44% at 2 years and 13% at 5 years [2]. Consequently, BO is one of the major obstacles to post-HSCT survival.

In the progression of BO, many risk factors, including respiratory tract infection and drug side effects can aggravate ventilation and cause respiratory failure [2]. Overcoming acute exacerbation of BO is crucial to improving its long-term prognosis. Pumpless extracorporeal interventional lung assist (iLA) is useful for supporting the pulmonary function in patients with severe hypercapnia and moderate hypoxia [3-6]. Here, we report on a patient with hypercapnic respiratory failure of BO after allogeneic peripheral blood stem cell transplantation (PBSCT) that was successfully overcome with iLA for the first time.

CASE

A 23-year-old female was diagnosed with acute lympho-
cytic leukemia (ALL) and underwent allogenic PBSCT after high-dose chemotherapy on 20 April 2011. Six months later, she developed an erythematous maculopapular skin rash, and a biopsy confirmed cutaneous GVHD. She also developed watery diarrhea with elevated serum liver enzymes, which suggested GVHD in the gastrointestinal tract and liver. After steroid pulse therapy, her symptoms and signs improved and she was kept on oral systemic steroid medication.

Twelve months after allogeneic PBSCT, she was admitted to the authors’ hospital with progressive shortness of breath and cough. A pulmonary function test revealed a severe obstructive pattern, with forced expiratory volume in one second (FEV₁) of 0.7 L, 20% of the predicted values, and a forced vital capacity (FVC) of 1.91 L, 43% of the predicted values. The FEV₁/FVC ratio was 37% (Fig. 1). Diffuse air trapping in both lungs and bronchial wall thickening and bronchiectasis observed on her chest computed tomography (CT) were compatible with BO (Fig. 2). Immune suppressants, including corticosteroid, were administered and her symptoms showed gradual improvement.

Five months later, she complained of severe dyspnea and fever, and there was expiratory wheezing throughout her lungs. A paranasal sinus X-ray showed right maxillary sinusitis, while a chest X-ray showed minimal peribronchial infiltration in the right lower lung field. She was treated with broad-spectrum antibiotics and bronchodilators without much improvement. Her dyspnea worsened, and an arterial blood gas analysis (ABGA) showed a pH of 7.19, PaCO₂ of 120 mmHg, PaO₂ of 169 mmHg. She was transferred to the Intensive Care Unit, and non-invasive ventilation was initially administered. However, her CO₂ retention worsened and she became stuporous. She was intubated immediately and placed on mechanical ventilation. Despite use of optimized ventilator care and neuromuscular blockade, her hypercapnia and respiratory acidosis worsened rapidly, and the peak airway pressure became elevated. Eventually, ABGA showed a pH of 7.12, PaCO₂ of 143 mmHg, PaO₂ of 139 mmHg. For immediate removal of CO₂, iLA was applied as rescue therapy. One hour after the iLA application, her hypercapnia showed a dramatic decrease. Six hours later, PaCO₂ had decreased to 85 mmHg while the pH increased to 7.38 (Fig. 3). A few hours later, the patient was extubated and supplied with oxygen via a high-flow nasal cannula. Her respiratory infection showed gradual improvement. She was successfully weaned off iLA for bronchiolitis obliterans after PBSCT.
off the iLA after 12 days. Without the iLA, the patient’s PaCO₂ and the pH remained stable (Fig. 3). She was transferred to a general ward the next day and was placed under hospice care.

**DISCUSSION**

BO is the most common late non-infectious pulmonary complication of allogeneic HSCT. The National Institutes of Health and other reviewers have published the clinical criteria for the diagnosis of BO. The criteria include (1) the absence of active infection in the respiratory tract, (2) a FEV₁ <75% of the predicted normal, (3) a FEV₁/FVC ratio <0.7 and a residual volume >120% of the predicted normal, and (4) evidence of air trapping, small airway thickening, or bronchiectasis on a high-resolution CT or pathologic confirmation of constrictive bronchiolitis. If a pathological diagnosis is not made, another manifestation of chronic GVHD is needed [7,8]. In the case presented, the patient met the criteria for the clinical diagnosis of BO even without a biopsy. Patients with BO often develop hypercapnia through an imbalance of the delicate respiratory dynamic state due to events such as infection or progression of the BO itself.

Despite the many clinical studies on treatment strategies for BO after HSCT, there is still no definitive treatment. Treatment of BO consists of corticosteroid and immunosuppressive drugs such as cyclosporine A or tacrolimus [9]. When the conventional immunosuppressive treatment is ineffective, the 2-year survival rate is 20% [10]. A few papers have recently reported on lung transplantation (LT) for BO complicated by HSCT, and suggested LT as an effective therapy for respiratory failure secondary to BO [9]. However, LT leads to high post-operative risk of rejection and infection, and finding a suitable lung donor is difficult. Despite these difficulties, LT is a feasible treatment option for refractory lung diseases such as BO [3]. In this case, however, the patient and her family preferred hospice care to LT.

Currently, iLA is an effective bridge to LT in patients with ventilation-refractory hypercapnia [3,4], and is widely used to rescue the patient from reversible hypercapnic respiratory failure, including asthma [5]. The iLA uses an arterio-venous approach without a pump and with an artificial membrane for CO₂ elimination, thus there is a limit to its application for treatment of severe hypoxemic and hemodynamically unstable patients. Nevertheless, iLA implantation is easier to perform and has significantly fewer side effects such as hemolysis, infection, renal insufficiency, and bleeding than extracorporeal membrane oxygenation (ECMO).

One case report demonstrated the usefulness of ECMO in overcoming hypercapnia in a BO patient [6]. Here, we report our experience with iLA for treatment of temporarily aggravated hypercapnia of BO after allogeneic PBSCT for ALL for the first time.

In conclusion, we successfully used iLA in a BO patient with life-threatening hypercapnia and respiratory acidosis. We emphasize that iLA is a highly effective therapeutic modality for overcoming reversible hypercapnic respiratory failure, including BO.

**CONFLICT OF INTEREST**

The authors have no financial conflicts of interest.

**REFERENCES**