

Allogeneic Hematopoietic Stem Cell Transplant Infusion During Venovenous Extracorporeal Membrane Oxygenation Support

BACKGROUND: Management of hematopoietic stem cell transplant complicated by respiratory failure has been facilitated by the use of extracorporeal membrane oxygenation as a bridge to curative chemotherapeutic options. This is the first report of hematopoietic stem cell transplantation on extracorporeal membrane oxygenation in the adult population.

CASE SUMMARY: A 28-year-old woman diagnosed with idiopathic aplastic anemia complicated by acute respiratory distress syndrome secondary to pneumonia required venovenous extracorporeal membrane oxygenation to supplement oxygenation and ventilation. She received hematopoietic stem cell transplantation while she was on extracorporeal membrane oxygenation support.

MAIN RESULTS AND CONCLUSION: Delivery of the stem cell through extracorporeal membrane oxygenation circuit was successful in the described patient. There was no sequestered stem cell in extracorporeal membrane oxygenation circuit, and she was found to have 90% donor chimerism suggesting successful engraftment. This report showed that infusion of stem cell through extracorporeal membrane oxygenation circuit is safe and feasible, and our results suggest that successful engraftment is possible.

KEY WORDS: acute respiratory distress syndrome; aplastic anemia; engraftment; extracorporeal life support; extracorporeal membrane oxygenation; hematopoietic stem cell transplantation

Hematopoietic stem cell transplantation (HSCT) is the curative treatment in idiopathic aplastic anemia (IAA) (1). Respiratory complications, resulting in acute respiratory distress syndrome (ARDS), may arise from the patient's immunocompromised status before HSCT (2, 3). Extracorporeal membrane oxygenation (ECMO) can also function as a bridge to HSCT in such condition (4, 5). The effect of the ECMO circuit and the oxygenator on the infused hematopoietic stem cells and on engraftment remains unclear. This report describes the process of HSCT for a patient supported with venovenous (VV) ECMO.

CASE PRESENTATION

We present a 28-year-old woman of Afro-Caribbean descent with no significant past medical or family history. The family consented to report her case. She presented with fatigue, palpitations, bruising, palate purpura, and epistaxis. Complete blood count study showed: hemoglobin 67 g/L (normal 135–175 g/L), platelet $34 \times 10^9/L$ (normal $140\text{--}450 \times 10^9/L$), and WBC $3.1 \times 10^9/L$

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(normal $4.5\text{--}11.0 \times 10^9/\text{L}$) with absolute neutrophil count $0.53 \times 10^9/\text{L}$ (normal $1.8\text{--}7.7 \times 10^9/\text{L}$). Bone marrow biopsy revealed a markedly hypocellular marrow for age (30–40% cellularity) with normal myeloid-to-erythroid ratio, decreased megakaryocytes, and absence of B-cell or T cell clonality. Heritable marrow failure syndromes were negative based on the blueprint bone marrow failure syndrome panel that uses next-generation sequencing technology. Full body positron emission tomography showed no fludeoxyglucose avidity.

The patient was diagnosed with severe IAA based on standard definitions and planned for allogeneic HSCT. The selected donor was her biological father as a haplo-identical donor. Unfortunately, the patient developed febrile neutropenia with *Enterobacter cloacae* bacteremia. The chest x-ray revealed multifocal pneumonia with pulmonary nodules. Bronchoalveolar lavage fluid yielded *Stenotrophomonas species* (“resistant to cotrimoxazole and levofloxacin”) that failed to respond to Tigecycline and Aztreonam. Pulmonary wedge biopsy of the pulmonary nodules demonstrated organizing pneumonia that was treated with prednisolone 1 mg/kg/d but resulted in a progression of the pulmonary infiltrates. The patient was admitted to the ICU for high-flow oxygen cannula (HFNC). Her pneumonia gradually deteriorated with worsening hypoxemia, which resulted in invasive mechanical ventilation after 2 weeks of HFNC. Her static lung compliance was 16 mL/cm H₂O while being ventilated with a volume-controlled mode at 6 mL/kg, positive end-expiratory pressure of 8 cm H₂O, and Fro_2 of 0.8. A recruitment maneuver was attempted, which was not beneficial and resulted in a pneumothorax (Fig. 1). After 48 hours of mechanical ventilation, inhaled nitric oxide, and paralysis, her $\text{PaO}_2/\text{FIO}_2$ remained at 75 with Pco_2 of 50 mm Hg and a driving pressure of 22 cm H₂O. Considering her young age, severe aplastic anemia, and related immunodeficiency, a multidisciplinary decision was made to proceed with HSCT with VV-ECMO as a bridge for respiratory support during the periengraftment period.

Five days following VV-ECMO implantation, she received nonmyeloablative conditioning with antithymocyte globulin, fludarabine, cyclophosphamide, and low-dose total body irradiation (4 Gy in two fractions) using the posttransplant cyclophosphamide graft-versus host disease prophylaxis platform. She received haploidentical HSCT infusion, as previously described

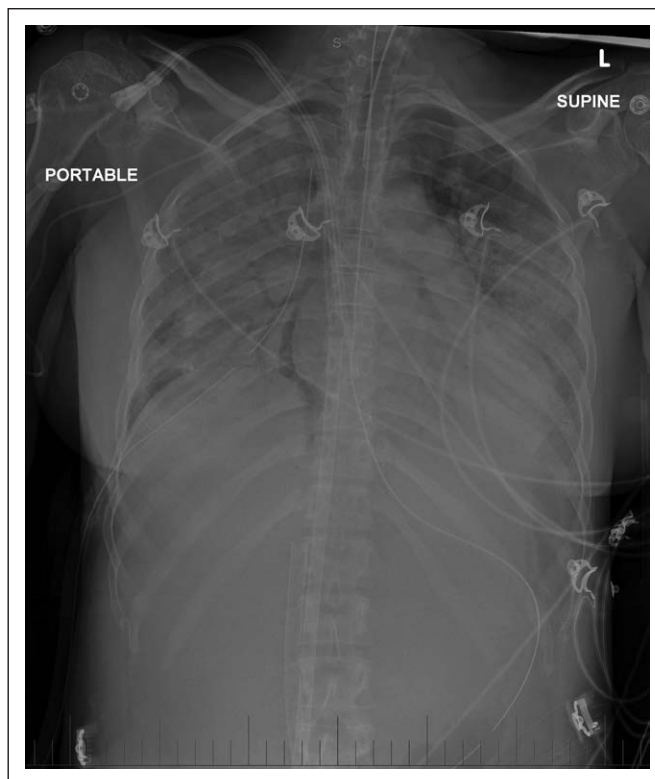


Figure 1. Chest x-ray showing bilateral diffuse consolidation. Right chest tube for pneumothorax.

by the Baltimore group (6), and remained on extracorporeal blood flow of 3.2 L/min throughout the conditioning regimen and while receiving the infusion of allogeneic HSCT. The infusion process is shown in Figure 2. A total of $10.75 \times 10^6/\text{kg}$ CD34+ cells (volume = 401 mL) (Table 1) were infused. ECMO flow could not be held because of the risk of respiratory

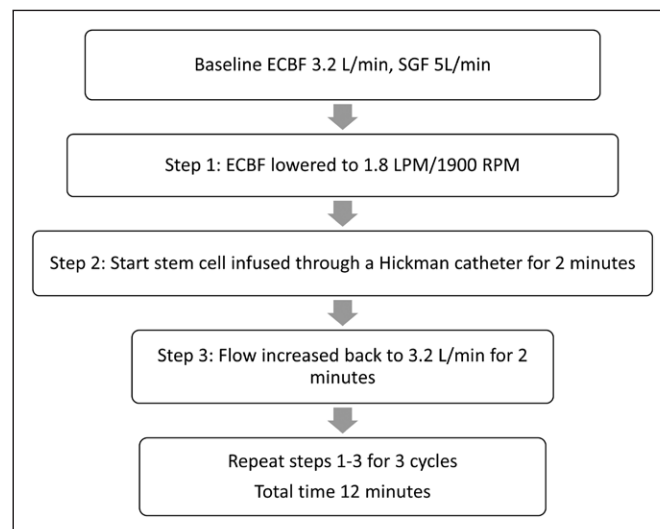


Figure 2. A proposed algorithm for optimal stem cell preservation during infusion on ECMO support.

TABLE 1.
The Stem Cell Infusion Volume and Extracted Cell From the Washout Fluid

Stem Cell Infusion Time	Stem Cell Volume Infused	Washout Volume	Extracted Cells From the Washout Volume
12 min	401.1	Bag 1: 483.3 mL	Bag 1: WBC $0.1 \times 10^9/L$ CD34+ cells 65.6
		Bag 2: 1776.2 mL	Bag 2: WBC 0.0 CD34+ cells not detected
		Bag 3: 1099.2 mL	Bag 3: WBC 0.0 CD34+ cells not detected

compromise. To maintain oxygen saturation above 90%, the patient was supported with ECMO blood flow of 3.2L/min, sweep gas flow of 11 L/min, and F_{do_2} of 100%. The stem cell infusion procedure was well-tolerated; nonetheless, the patient experienced a vasoplegic shock 6 hours after the infusion. The differential diagnosis consisted of immune reconstitution inflammatory syndrome, cytokine release syndrome (due to cyclophosphamide), and sepsis. Antibiotics dose was increased, and tocilizumab was given, which resulted in complete resolution of the vasoplegic state within 24 hours.

To assess for the presence of trapped HSCT in the ECMO circuit, on day 3 post-HSCT, the circuit was changed, and 3358 mL of irrigated fluid was extracted. A CD34 cell count was performed by flow cytometry and did not reveal any quantifiable amount of CD34 positive hematopoietic stem cells in the irrigated fluid from the circuit/membrane washout (Table 1). Unfortunately, the patient deteriorated and passed away from septic shock 15 days after HSCT. Donor chimerism study on day 7 showed mixed donor chimerism with 75% of polymorphonuclear cells being of donor origin and 80% of lymphoid (mixed lymphoid lineage cells) cells being of donor origin, and showed 90% chimerism on day 14. This finding suggests that, if given more time, donor engraftment with reconstitution of peripheral blood counts would have almost occurred.

DISCUSSION

This is a case of IAA complicated by ARDS secondary to *Stenotrophomonas maltophilia* pneumonia requiring VV-ECMO after a failure of conventional therapy for ARDS. In the context of the aggressiveness of the

disease and the age of the patient, HSCT as a curative intent was performed (7). Following stem cell infusion, washout of the ECMO circuit and membrane revealed no lingering stem cells. The patient was found to have 90% donor chimerism, both suggesting that delivery of stem cell through ECMO circuit is feasible, and if more time was allowed, the patient would have successfully engrafted.

Although HSCT is a lifesaving procedure, it has a high risk of adverse events. In the ECMO population, the risk becomes higher as we lack the knowledge of delivery of stem cells through adult ECMO circuits and the optimal dose of conditioning chemotherapy (8). To date, there is only one case report, which showed successful engraftment of HSCT through venoarterial ECMO circuit in a 15-month-old child with Wiskott-Aldrich syndrome (9). As the described patient was an adult, it was anticipated that higher ECMO flow would result in cell lysis and cell sequestration in the oxygenator, and the pharmacokinetics of preconditioning chemotherapy regimen maybe variable when delivered during ECMO support. Therefore, a higher dose of preconditioning chemotherapy and decreased ECMO flow during the period of delivery was performed (Fig. 2). Flow cytometry demonstrated no stem cells on the extracted volume from the ECMO circuit suggesting that stem cells do not sequester in the ECMO oxygenator membrane or the circuit; the procedure was performed as follows: from the irrigated bag, we took 50 mL and spun tube and resuspended the buffy coat, calculated number of CD34 cells and total nucleated cell count, and then extrapolated calculation from a 50-mL sample to 483-mL bag; the same was done for the other bags.

Knowing that HSCT through ECMO circuits is feasible, a specialized multidisciplinary team consisting of hematologist, ECMO specialist, nurses, perfusionist,

and pharmacist is paramount. Keeping in mind poor outcome among patients requiring ECMO, careful patient selection will certainly improve short- and long-term outcomes.

CONCLUSIONS

This is the first report addressing feasibility of infusion of stem cells through an ECMO circuit in the adult population. It emphasizes a cell-preserving infusion strategy orchestrated by a multidisciplinary medical team.

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