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Successful Use of Extracorporeal Life Support in a Hematopoietic Stem Cell Transplant Patient with Neuroblastoma

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Abstract: Respiratory failure associated with hematopoietic stem cell transplantation (HSCT) has been considered a contraindication for use of extracorporeal membrane oxygenation (ECMO) at many centers. We describe a child with neuroblastoma and hypoxemic respiratory failure following HSCT who was successfully managed with veno-venous (VV) ECMO. The patient was an 18-month-old female with high-risk neuroblastoma status post tumor resection, chemotherapy, autologous HSCT, and primary site radiation. On day 113 posttransplant while receiving maintenance immunotherapy, she had an acute respiratory decompensation because of rhinovirus, aspiration pneumonia, and capillary leak syndrome. The patient was intubated and transitioned to a high frequency oscillatory ventilation and inhaled nitric oxide. Because of refractory hypoxemia, she was cannulated for VV ECMO. She was weaned and decannulated after 7.5 days on ECMO, then subsequently transferred for inpatient rehabilitation. The most recent Extracorporeal Life Support Organization registry analysis showed low survival (3/29) in patients requiring ECMO after HSCT, and 2 of 3 survivors had nononcological diagnoses. However, our patient's outcome suggests that HSCT status should not be an absolute contraindication. The presence of a reversible single organ failure and the absence of significant bleeding risk in an engrafted, neurologically intact, and non-neutropenic HSCT patient with a favorable prognosis can support the potential benefit of ECMO. **Keywords:** acute respiratory failure, malignancy, neuroblastoma, hematopoietic stem cell transplantation, extracorporeal membrane oxygenation. *J Extra Corpor Technol. 2018;50:61–64*

OVERVIEW

The use of extracorporeal membrane oxygenation (ECMO) in patients after hematopoietic stem cell transplantation (HSCT) who develop subsequent acute respiratory failure (ARF) remains controversial, and HSCT status is often considered a contraindication for the use of ECMO at many centers (1,2). We describe a child with high-risk neuroblastoma and severe hypoxemic respiratory failure after HSCT who was successfully managed with veno-venous (VV) ECMO support.

DESCRIPTION

An 18-month-old female developed fever up to 40°C, large left-sided occipital and midline abdominal mass and hematuria. The intracranial lesion caused a significant compression of the cerebellar hemisphere and obstruction of the 4th ventricle, leading to hydrocephalus. She underwent a craniotomy for tumor biopsy and resection. The abdomen CT showed a large left adrenal mass with extensive retroperitoneal nodal masses occupying both sides of the abdomen with hepatic and left renal metastases. Biopsies revealed high-risk neuroblastoma. A *meta-iodobenzylguanidine* scan showed extensive osseous metastatic disease and bone marrow testing showed the presence of neuroblastoma, putting her in the stage 4 category. Because of her age and initial disease characteristics, she was classified as intermediate-risk and cycle 1 of her chemotherapy was administered per Children's Oncology Group (COG) protocol ANBL0531. Subsequent tumor testing detected MYCN amplification, which moved her into the high-risk classification and required intensification of her therapy to be given per COG ANBL0532. This involved six cycles of intensive, multi-agent induction chemotherapy, and resection of her primary tumor (a 4 × 4 cm left adrenal mass). Repeat imaging after induction therapy suggested a complete response. As part of consolidation therapy, she underwent

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a single autologous HSCT after high dose chemotherapy with carboplatin, etoposide, and melphalan (CEM), followed by radiation to her primary tumor bed. After consolidation, she was started on maintenance therapy per ANBL0032 protocol. This regimen consisted of dinutuximab, a chimeric antidisialoganglioside (GD2) monoclonal antibody (ch14.18), with GM-CSF and interleukin-2 (IL-2) to augment the immune response, along with isotretinoin.

On day 113 posttransplant while receiving her second cycle of maintenance immunotherapy with dinutuximab and IL-2 (hospital day 4), she developed a rhinovirus respiratory tract infection with subsequent aspiration pneumonia, capillary leak syndrome, and ARF. She was transferred to the pediatric intensive care unit (PICU), intubated, and mechanically ventilated. Chest radiograph (Figure 1A) revealed diffuse bilateral pulmonary infiltrates. She was quickly transitioned to a high frequency oscillatory ventilation with inhaled nitric oxide. Because of severe hypoxemia and a persistently high oxygenation index (up to 62), discussion for ECMO candidacy was initiated. Despite being high risk, we thought this patient was a reasonable candidate for ECMO support for the following reasons: she had received an autologous HSCT (thus no graft-vs-host disease) with engraftment, had single organ failure (lungs) due to likely reversible causes (viral infection and time-limited capillary leak syndrome), was neurologically intact, was not neutropenic, and had no significant risk of bleeding. In addition, from an oncologic standpoint, her prognosis was favorable.

She was cannulated for VV ECMO support via the right internal jugular vein with a 19-French bicaval dual lumen cannula (Avalon Elite; Maquet Cardiovascular, Wayne, NJ). The ECMO flow was initiated with a centrifugal pump and a polymethylpentene membrane oxygenator (Quadrox; Maquet Cardiovascular). The flow was initiated and increased to a maximum rate of 1,330 mL/min (120 mL/kg/min) over 20 minutes. Her blood arterial oxygen saturation quickly improved after ECMO cannulation. The patient required flows between 90 and 100 mL/kg/min to maintain adequate oxygenation. Initially, she was placed on rest ventilator settings of pressure-control ventilation (PCV) with peak inspiratory pressure (PIP) 20, positive end expiratory pressure (PEEP) 10, inspiratory rate 10, pressure support (PS) 10 mmHg, and fraction of inspired oxygen (FiO_2) 30%.

During her ECMO run, therapeutic bronchoscopy (on days 5 and 6) was used for lung recruitment and removal of secretions. Biventricular mildly depressed cardiac function noted by echocardiography was managed with a milrinone infusion. Continuous veno-venous hemofiltration (CVVH) was initiated via the ECMO circuit for fluid management (while patient maintained good urine output). She was empirically treated with broad spectrum antibiotics (vancomycin and piperacillin/tazobactam) as well as fluconazole for a respiratory culture growing *Candida albicans*. There were no significant bleeding episodes. Heparin infusion was maintained at 35 units/kg/h, with a goal activated clotting time of 160–180 seconds and an anti-Xa assay between .3 and .7 U/mL. After a successful O_2 challenge test and capping trial (Figure 1C), she was weaned and decannulated from ECMO after 7.5 days. At decannulation, patient ventilator settings included PCV PIP 30, PEEP 8, rate 26, PS 10, and FiO_2 30%. The CVVH was stopped after ECMO decannulation. She was extubated 3 days later and subsequently transferred to inpatient rehabilitation on hospital day 23. The patient subsequently completed all therapy for neuroblastoma and remains in remission 18 months later.

COMMENT

Controversy persists regarding the use of extracorporeal support in children and adults status post-HSCT who fail conventional ventilator support. Recently, Staudacher and

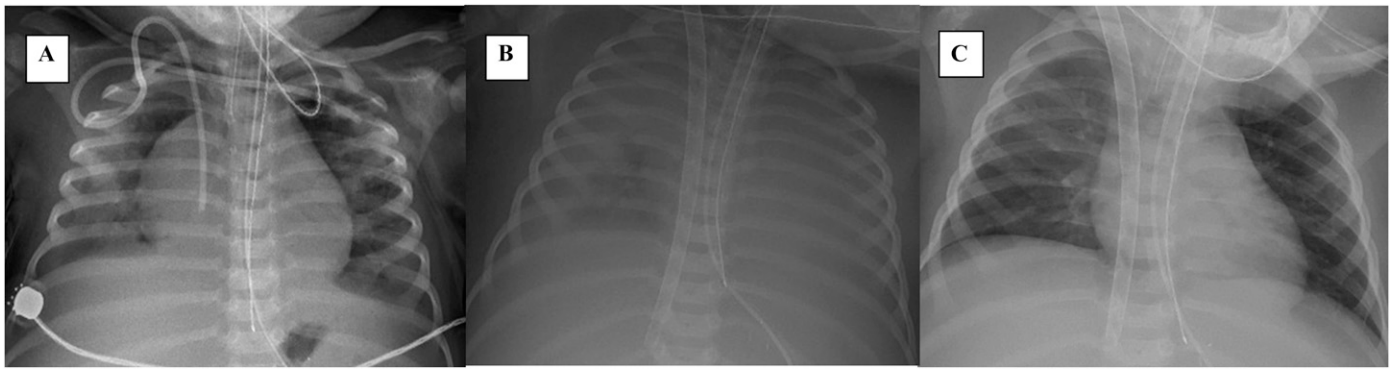

Figure 1. Patient's chest radiographs over the course of treatment. (A) Before ECMO cannulation, showing bilateral airspace opacities consistent with pneumonia along with a right-sided pleural effusion. (B) Shortly after ECMO cannulation, showing bilateral complete opacification of the lungs with ECMO cannula in the inferior vena cava. (C) On the day of ECMO decannulation, showing re-expansion of the lungs which are relatively free of infiltrate.

colleagues argued in support of consideration, noting that HSCT patients are often young and their underlying disease is potentially cured by stem cell transplantation. In their experience, 2/13 (15%) patients survived to ICU discharge (1). Schmidt and colleagues argued that the HSCT status in ARF was an absolute contraindication for extracorporeal support (2) citing a series with four HSCT patients who all died after receiving ECMO for ARF (3).

Previous retrospective database reviews have suggested very poor outcomes with HSCT and ECMO use. Two previous analyses of pediatric experience from the Extracorporeal Life Support Organization (ELSO) registry have been published. From 1991 to 2004, 19 pediatric patients status post-HSCT were placed on ECMO (17 for pulmonary support). Four patients survived to ECMO decannulation and only one survived to hospital discharge (5% survival) (4). In this cohort, 12 patients had allogeneic HSCT and four had autologous HSCT. The procedures provided for the other patients were not described. The single patient who survived to discharge had lymphoma and received an autologous HSCT. In an updated analysis of the ELSO registry from 1991 to 2012, 29 pediatric patients received ECMO support after HSCT (5). Six patients survived to ECMO decannulation and three patients survived to hospital discharge (10% survival). However, this new analysis did suggest that of the 10 additional ECMO/HSCT patients, two survived (20%). Only one of the additional six patients had an oncologic diagnosis (e.g., acute lymphoblastic leukemia) with respiratory failure due to respiratory syncytial virus. Four patients had a hematologic diagnosis and one patient had a disorder of metabolism. The type of HSCT performed was not specified in this review.

Another case report, not included in the previous ELSO registry analyses, discussed using ECMO in a pediatric neuroblastoma patient after an autologous HSCT with neutropenia, sepsis, and acute hemodynamic instability (6). ARF was not the primary reason for initiating ECMO. The patient successfully survived to decannulation and discharge. The authors discussed the ethical dilemma surrounding making this difficult decision in the absence of clinical evidence of efficacy in the scenario and emphasized the value of assessing each HSCT patient on an individual basis.

Authors in previous reviews and editorials discussed ECMO use for HSCT patients who had received either allogeneic or autologous transplants (1–6). Our pediatric patient received an autologous HSCT. The treatment-related morbidity and mortality of HSCT is significantly lower in patients undergoing autologous compared with allogeneic transplants. This is in large part due to the potential impact of acute graft vs. host disease, which is a risk only in the allogeneic patient. For instance, treatment-related mortality of HSCT in a cohort of 355 neuroblastoma patients who underwent either single or tandem autologous transplant was only 2.8% (7). Similar data are seen in other pediatric patients with solid tumors who underwent autologous HSCT (8). Of course, there is not enough experience to compare the outcomes of patients undergoing ECMO in allogeneic compared with autologous HSCT.

We suggest that our current patient was a reasonable candidate for ECMO support for the reasons stated earlier: an autologous HSCT recipient with engraftment and reasonable prognosis, single organ failure due to potentially reversible causes, neurologically intact, not neutropenic, and no significant risk of bleeding. Also, high-risk neuroblastoma patients who receive a single autologous transplant with CEM therapy who go on to complete their immunotherapy have a favorable prognosis (3-year overall survival of 76%), we thought that aggressive measures were warranted (7). We suspected that our patient's ARF was largely due to a combination of rhinovirus infection and cytokine-mediated capillary leak syndrome, a phenomenon occurring in 23% of patients receiving this immunotherapy, particularly during the cycles (2 and 4) containing IL-2 (9). The symptoms of capillary leak are typically self-limited and resolve soon after the cessation of treatment, if the patient can be adequately supported through the acute phase. Our team determined that ECMO support could provide the appropriate platform for lung recovery and rest from the multiple etiologies of respiratory failure.

Our case experience suggests that with careful patient selection, ECMO can potentially provide a platform to support lung recovery and rest in the HSCT patient. Cumulative case experience still argues against routine ECMO use in the HSCT patient. However, the presence of HSCT should not serve as an absolute contraindication for ECMO use. Future studies should analyze outcomes post-ECMO based on the type of transplant (allogeneic vs. autologous) and underlying oncologic diagnosis. Factors including the underlying diagnosis, type of HSCT, presence of potentially reversible single organ failure, absence of neutropenia, absence of bleeding risk, and favorable overall prognosis should lead to consideration for use of ECMO.

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