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Brief Report

Case report and review of the literature: the utilisation of a ventricular assist device as bridge to recovery for anthracycline-induced ventricular dysfunction

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Abstract Ventricular assist devices are used in children with heart failure as a bridge to myocardial recovery or cardiac transplantation. Anthracyclines cause cardiac toxicity and may result in acute or long-term cardiac failure. We describe the use of a ventricular assist device as a bridge to recovery in a child with severe acute anthracycline-induced cardiomyopathy, and we review the associated literature. A 6-year-old girl was treated for acute myeloblastic leukaemia with daunorubicin and mitoxantrone. After 2 weeks her final dose of chemotherapy, her Left Ventricular Ejection Fraction decreased to 21%. Despite initiation of medical therapy, she had continued deterioration of left ventricular function and developed evidence of poor end-organ perfusion. She was not a candidate for cardiac transplantation, as the post-transplant immune suppression therapy would put her at risk for recurrence of her malignancy. We placed her on a short-term ventricular assist device as a bridge to ultimately placing her on a long-term ventricular assist device versus continuing medical therapy. Her left ventricular ejection fraction improved to 55% 24 days after ventricular assist device insertion. She was separated from the ventricular assist device 26 days after its insertion. She was discharged home 29 days later and is now 28 months after ventricular assist device implantation with stable ventricular function, as documented by a left ventricular ejection fraction of 55%, and normal end organ function. This case is one of the only reports known describing successful use of a short-term ventricular assist device as a bridge to recovery in a child with severe acute anthracycline-induced cardiotoxicity.

Keywords: Ventricular assist device; cardiotoxicity; chemotherapy-induced cardiomyopathy; surgery

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Background

Ventricular assist devices have been used in patients with cardiac failure as a bridge to myocardial recovery, destination therapy, or cardiac transplantation. As technology has evolved, allowing ventricular assist devices to be used in smaller patients, their use in children is increasing. Anthracyclines and anthracenediones can cause cardiac toxicity and may result in acute and chronic congestive heart failure. We describe the use of a left ventricular assist device as a bridge to recovery in a child with severe acute anthracycline-induced cardiomyopathy, and we review the associated literature.

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Case

A 6-year-old girl was treated for acute myeloblastic leukaemia according to the Children's Oncology

Group (COG) AAML1031 protocol,[1] receiving four cycles of chemotherapy from December, 2013 to April, 2014, with a combination of cytarabine, etoposide, daunorubicin, and mitoxantrone, with a cumulative doxorubicin isotoxic dose of 381.6 mm/m^2 (body surface area was 0.9 m^2). She underwent serial echocardiograms during her treatment, documenting normal left ventricular dimensions and systolic function, with a left ventricular ejection fraction of 60–72%. After 80 days completing her final dose of chemotherapy, a routine echocardiogram showed her left ventricular ejection fraction to be 44%, and she was started on oral enalapril and furosemide. Over the next 9 days, she developed increased work of breathing and shortness of breath. A repeat echocardiogram showed a decrease in left ventricular ejection fraction to 21%. She was then started on a milrinone infusion and intravenous furosemide. Viral polymerase chain reaction was positive for Human Herpesvirus 6, 922 copies, and she was treated with a total of 2 g/kg of intravenous immunoglobulin over four doses for possible viral myocarditis. Despite these treatments, by post-chemotherapy day 25, she had continued deterioration of left ventricular systolic function with an ejection fraction of <10%. She had evidence of poor end-organ perfusion, with respiratory failure, decreased urine output (<2 ml/kg/hour), and hepatic dysfunction (transaminases >2000), although her right ventricular systolic function by echocardiography was normal. An urgent multidisciplinary conference was held to obtain consensus about treatment for her cardiac failure. As she had just completed chemotherapy, she was not considered a candidate for cardiac transplantation, as the post-transplant immune suppression therapy would put her at significant risk for recurrence of her malignancy. However, she had a favourable prognosis for her malignancy, because the overall survival of acute myeloblastic leukaemia is 60–80%, and event-free survival is 45–55%. After multidisciplinary discussion, we elected to place her on a short-term left ventricular assist device, which is approved for up to 30 days. This would provide a time period of cardiac stability to allow her to either recover or become a good candidate for a longer-term ventricular assist device.

Our patient was placed on a CentriMag (Thoratec Corporation, Pleasanton, California, United States of America) continuous-flow device on post-chemotherapy day 31. While on the ventricular assist device, we were able to provide a cardiac index of 2.5 to 2.8 litres per minute. The anticoagulation regimen we used for this patient included unfractionated heparin with target activated clotting time of 160 to 180 and activated partial thromboplastin time of 1.5 to 2 times control. After 48 hours, she was also started on anti-platelet therapy with aspirin, and platelet function was monitored with thromboelastography with platelet mapping, with aspirin doses adjusted using the Edmonton protocol.[2,3] On ventricular assist device day 2, she required initiation of inhaled nitric oxide for right ventricular support because of echocardiographic evidence of right ventricular dilatation and dysfunction. Milrinone and low-dose Epinephrine (0.03 mcg/kg/minute) infusions were also continued for right ventricular support, and she was eventually transitioned from nitric oxide to tadalafil for pulmonary vasodilatation. She showed recovery of end-organ perfusion with decreased liver transaminase levels (<100) and improved renal function. She was extubated after 8 days on the ventricular assist device. She developed ectopic atrial tachycardia that required discontinuation of the low-dose epinephrine and initiation of amiodarone to treat the arrhythmia. The left ventricular systolic function gradually improved, and 24 days after ventricular assist device implantation her left ventricular ejection fraction was 55%. Subsequently, the ventricular assist device flows were gradually weaned under echocardiographic surveillance, and left ventricular ejection fraction remained above 50% with these trials. On ventricular assist device day 26, she was re-started on epinephrine 0.05 mcg/kg/minute and milrinone 1 mcg/kg/minute in preparation for decannulation. She was then successfully separated from the ventricular assist device. She was discharged home 29 days after ventricular assist device explantation (86 days after chemotherapy completion) on aspirin, carvedilol, digoxin, enalapril, furosemide, spironolactone, tadalafil, levocarnitine, and ubiquinone. She has been home for 28 months after ventricular assist device implantation with stable left ventricular ejection fraction of 55–60% and with normal end organ function, including pulmonary, renal, hepatic, and neurological function.

Discussion

Anthracyclines have significant antitumour activity, play a major role in combination chemotherapy, and are used in over 50% of paediatric protocols.[4] However, one of the potentially serious side effects of anthracyclines is cardiotoxicity, as they can cause irreversible cardiac injury by causing myocardial cell death. A cumulative dose of greater than 550 mg/m^2 has a significantly increased risk of anthracycline-induced cardiomyopathy; however, cardiomyopathy may occur at even much lower doses. Anthracyclines can cause asymptomatic cardiac dysfunction with decreased left ventricular contractility, or evidence of left ventricular diastolic dysfunction. Symptoms of clinical heart failure include pulmonary and peripheral oedema, dyspnoea, poor feeding, hepatomegaly, and decreased exercise tolerance.[5,6] Early or acute toxicity occurs during therapy or in the 1st year

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following therapy, whereas late cardiotoxicity occurs at least 1 year after the completion of therapy.[5–7] No specific treatment exists for anthracycline-induced cardiotoxicity other than supportive care, although some patients show variable recovery of ventricular function with conventional medical therapy for heart failure.

Mitoxantrone hydrochloride, an anthracenedione, is a non-cell-cycle-specific anthraquinone derivative, which has demonstrated significant antitumour activity similar to anthracyclines; unfortunately, in clinical studies, mitoxantrone has been shown to cause anthracycline-like cardiotoxicity.[8,9] In a systematic review of 17 cohort studies, Van Dalen et al reported a cumulative incidence of mitoxantrone-induced cardiomyopathy ranging from 0 to 6.7% for clinical heart failure and from 0 to 80% for asymptomatic cardiac dysfunction.[7] These findings compare to a cumulative incidence of anthracycline-induced cardiotoxicity ranging from 0 to 16% for symptomatic heart failure and from 0 to 57% for asymptomatic cardiac dysfunction.

Ventricular assist devices may serve as a bridge to recovery, as a bridge to transplantation, or for permanent cardiac support.[10] The use of ventricular assist devices in children has been described as a bridge to cardiac transplantation or recovery of ventricular function in various forms of paediatric heart failure.[11–15] There are short-term and long-term ventricular assist devices that are available based upon the patient's size and presumed duration of therapy. Short-term devices are typically used for up to 14 days, but can used for up to 30 days. Jefferies et al discussed the use of a short-term device as a bridge to decision, during which time the patients have an opportunity to recover or have their transplant candidacy determined.[14] If there is no sufficient recovery while on the short-term device, the patient can be transitioned to a long-term device.[11,14,15] The determination of appropriate timing of transition from a short-term ventricular assist device to a long-term ventricular assist device may be challenging. This transition is often made between 14 and 30 days after insertion of the short-term ventricular assist device, and is often guided by the clinical status of the patient, as well as the presence or absence of evidence of ventricular recovery. As discussed above, our patient had solid evidence of ventricular recovery by 24 days after implantation of the short-term ventricular assist device; her left ventricular systolic function gradually improved, and by 24 days after implantation of the short-term ventricular assist device her left ventricular ejection fraction was 55%. Therefore, in our patient, because of evidence of progressive ventricular recovery, we elected not to transition to the use of a long-term ventricular assist device.

Successful bridge to recovery with ventricular assist device implantation for anthracycline-induced cardiomyopathy has been described in adults.[16] Very little has been published to date regarding the use of ventricular assist devices in children with anthracycline-induced cardiac toxicity. In 2013 and 2014, Schweiger et al and Cavigelli-Brunner et al published two case reports describing the use of a long-term ventricular assist device in an 8-year-old patient with a body surface area of 0.97 m^2 who had severe acute anthracycline-induced cardiomyopathy.[17,18] These reports described the implantation of a long-term ventricular assist device[17] and the subsequent successful explantation after recovery.[18] In their patient, they implanted a HeartWare™ Ventricular Assist System (https://www.heartware.com/). The patient was discharged home with the ventricular assist device in place after 90 days, and underwent successful explantation at 149 days after implantation. They described their weaning protocol, including performing a right heart catheterisation before explantation. Follow-up on their patient was 4 months after device explanation.

Another report by Freilich et al[19] describes the clinical course of a 16-year-old girl in remission from lymphoma who developed cardiogenic shock owing to a severe anthracycline cardiomyopathy. The patient was initially stabilised using central extracorporeal membrane oxygenation support, followed by conversion to a left ventricular assist device. Unexpected evidence of cardiac recovery 9 months after implantation allowed for weaning from the left ventricular assist device over three months with successful device explantation one year after implantation. The authors reported that the patient was alive 18 months after explantation in New York Heart Association class I, on conventional heart failure medical management and metabolic therapy.

In our patient, we presumed that her cardiomyopathy and heart failure was caused by acute anthracycline cardiotoxicity, because of the proximity of her prior chemotherapy. Her course may have also been complicated by viral myocarditis from Human Herpesvirus 6, although her condition continued to deteriorate despite treatment with intravenous immunoglobulin and optimisation of therapy for cardiac failure. The use of a short-term ventricular assist device afforded us the opportunity to support this patient, and allow for potential recovery of left ventricular function. Our original plan was to use the ventricular assist device for up to 30 days – as approved by the Food and Drug Administration for the Centrimag device – as a bridge to recovery and explantation, versus decision to convert to a longer-term ventricular assist device as a bridge to cardiac transplantation when her risk of recurrence of malignancy was considered acceptable

to proceed. Fortunately, our patient showed recovery of left ventricular function, evidenced by improved left ventricular ejection fraction, decreased left ventricular end diastolic diameter, as well as normalisation of end organ function. This enabled us to successfully explant her ventricular assist device.

In addition to standard medical management, mechanical circulatory support, and cardiac transplantation, a variety of other therapeutic strategies have been studied that may be applicable to selected patients with heart failure.[20,21] These strategies include first, reversible pulmonary artery banding in left ventricular-dilated cardiomyopathy with preserved right ventricular function; second, the creation of restrictive inter-atrial communication; third, atrioseptostomy or reverse Potts shunt in pulmonary arterial hypertension; and finally, return to a foetal, parallel circulation by combining atrioseptostomy and reversed Potts shunt with or without placement of a bilateral pulmonary artery banding. Although all of these novel approaches may be beneficial in select patients, the mainstay of therapy for cardiac failure in children and adults is medical management, mechanical circulatory support, and cardiac transplantation.

Conclusion

We describe the use of a short-term ventricular assist device as a bridge to recovery in a child with acute Mitoxantrone cardiotoxicity and possible Human Herpesvirus 6 myocarditis. Our experience suggests that short-term ventricular assist devices may be used in select children with acute anthracycline cardiotoxicity as a bridge to recovery or decision.

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None.

Authors' Contributions: Drs S.S., G.S., and A.A.-K. determined that this would be a unique case report to publish. Dr S.S. is the primary Oncologist for this patient. Dr G.S. was the primary Cardiologist for this patient. Dr A.A.-K. is the medical director of the Heart Failure/Transplant program. Dr J.J. is the Chief of Cardiovascular Surgery and Surgical Director of Heart Transplantation and Extracorporeal Life Support Programs. They have reviewed and revised the manuscript. They have approved the final manuscript as submitted. D.K., J.C., and M.D. participated in the care of this patient.

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Conflicts of Interest

None.

Ethical Standards

Informed consent was obtained from the patient's family for the use of the ventricular assist device.

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