MAYO CLINIC

CASE REPORT

Cell-Based Therapy for Myocardial Dysfunction After Fontan Operation in Hypoplastic Left Heart Syndrome

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Abstract

Myocardial dysfunction after Fontan palliation for univentricular congenital heart disease is a challenging clinical problem. The medical treatment has a limited impact, with cardiac transplant being the ultimate management step. Cell-based therapies are evolving as a new treatment for heart failure. Phase 1 clinical trials using regenerative therapeutic strategies in congenital heart disease are ongoing. We report the first case of autologous bone marrow–derived mononuclear cell administration for ventricular dysfunction, 23 years after Fontan operation in a patient with hypoplastic left heart syndrome. The cells were delivered into the coronary circulation by cardiac catheterization. Ventricular size decreased and several parameters reflecting ventricular function improved, with maximum change noted 3 months after cell delivery. Such regenerative therapeutic options may help in delaying and preventing cardiac transplant.

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Staged surgical palliative procedures culminating in a Fontan circulation represent the standard of care for most patients with functionally single ventricles, such as those with hypoplastic left heart syndrome (HLHS). Long-term complications of the Fontan procedure include myocardial dysfunction secondary to multiple factors including prolonged increased workload, leading to heart failure requiring cardiac transplant in many cases.[1] With the growing population of patients with Fontan palliation and the relatively unchanged limited availability of organs for transplant, it is imperative that alternative treatment strategies be sought. Medical treatment of heart failure with afterload-reducing agents and other medications used in structurally normal myopathic hearts has not shown clear benefit in these patients. Cell-based therapies, primarily using bone marrow–derived cells, have been tested in clinical trials for adults with ischemic heart disease[2-22] and nonischemic dilated cardiomyopathy[23-25] for many years. These studies are now being applied in children and adults with congenital heart disease. However, the utility, safety, and efficacy of cell-based therapies are not established in these patients. We have initiated a phase 1 clinical trial (NCT 02549625) for use of bone marrow–derived mononuclear cells (BM-MNCs) in Fontan procedure–treated patients with myocardial dysfunction. The mononuclear cell preparation is a heterogeneous mixture of cells containing CD34 progenitor stem cells thought to promote myocardial regeneration through paracrine mediators. We report the first case of intracoronary delivery of autologous BM-MNCs for single

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right ventricular dysfunction after Fontan palliation.

REPORT OF CASE

The patient presented for enrollment in our cell therapy clinical trial at age 25 years with clinical heart failure symptoms. He was born with HLHS (mitral and aortic valve stenosis, severely hypoplastic left ventricle, and ascending aorta). His surgical history consisted of Norwood operation at age 1 month followed by hemi-Fontan procedure at age 4 months, and finally creation of a nonfenestrated, lateral tunnel-type Fontan connection at an early age (18 months). At age 20 years, he began to experience dyspnea with activity that progressed over the next 2 years. One year after the onset of symptoms, obvious ascites developed. He did not have enteric protein loss or hypoalbuminemia but was found to have severe regurgitation of the neoaortic valve and severe right (systemic) ventricular systolic dysfunction. He underwent a number of procedures and trials of medical therapy, including embolization of aortopulmonary collaterals, catheter dilation/stenting of the left lower pulmonary vein and left pulmonary artery, and a course of intravenous inotropic support, with no lasting change in symptoms or ascites. He was evaluated for cardiac transplant because he was not a candidate for surgical replacement of neoaortic valve due to severe ventricular dysfunction with estimated ejection fraction (EF) of 15%. Evaluation revealed marked prior sensitization to human leukocyte antigens (85% unacceptable antigen profile), creating a prohibitive risk for cardiac transplant. Medical treatment was subsequently optimized with multiple drugs including enalapril, carvedilol, digoxin, and diuretics. The doses were escalated over several months to the maximum tolerated by the patient. He had resolution of most of his symptoms within a period of 4 to 6 months. He remained clinically stable over the next 2 years. However, his right ventricle (RV) remained severely dilated because of persistent neoaortic regurgitation, and ventricular EF remained moderately decreased at 30% to 35%. Despite these improvements, the risk of aortic valve replacement was still felt to be prohibitive. Transcatheter neoaortic valve replacement was not possible because of the massively dilated neoaortic root, which was larger than any available device. Pacemaker therapy was not attempted as an isolated approach because the risk of epicardial placement was felt to outweigh the benefit of restoring heart rate response in the setting of his dysfunction and previous cardiac operations.

At age 25 years, the patient was enrolled into the phase 1 clinical trial using BM-MNCs in patients with myocardial dysfunction after Fontan procedure (NCT 02549625). Preenrollment screening revealed an increased N-terminal pro-B-type natriuretic peptide (NT-proBNP) level of 503 pg/mL (normal, <51 pg/mL), with a normal creatine kinase-MB (CK-MB) level and undetectable cardiac troponin T. Baseline C-reactive protein was normal. Holter monitoring revealed sinus bradycardia (heart rate range, 32-69 beats/min) with multiple pauses, the longest being 3.11 seconds. There was a short 10-beat run of supraventricular tachycardia at a rate of 111 beats/min and occasional (<1%) ventricular and supraventricular ectopic beats. Transthoracic echocardiography revealed severe RV enlargement with estimated EF of 30% to 35%. Cardiac magnetic resonance (CMR) imaging identified an RV end-diastolic volume of 213 mL/m^2 and calculated RV EF of 34%. The origins and proximal courses of the coronary arteries were normal on CMR imaging.

Under deep conscious sedation and local anesthesia, 75 mL of bone marrow was aspirated from the iliac spine and collected in a heparinized collection bag. The bone marrow aspirate was transported to the Human Cell Therapy Laboratory at Mayo Clinic, where it was stored at refrigerated temperature (2°C-8°C) and processed to obtain the mononuclear cell fraction using a Ficoll density gradient closed system the following day. The final dose of 2×10^6 cells/kg (94% viability) was suspended in 12 mL of 2.5% human albumin in Plasma-Lyte A. The Gram stain was negative and cultures (aerobic and anaerobic) remained negative for 14 days.

Cardiac catheterization was performed after the cells were processed and passed quality control. Bivalirudin was used for anticoagulation during the procedure instead of heparin to avoid potential disruption of cell migration and engraftment.[26] Hemodynamic assessment revealed a mean pressure of 16 mm Hg in Fontan circuit and a transpulmonary gradient of 1 mm Hg, both of which were normal.

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