The Emergence of Stem Cell Therapy for Patients With Congenital Heart Disease

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Stem cell therapy has emerged as one of the most highly investigated new therapies for cardiovascular disease. Given the enormous health care and economic burden imposed by congestive heart failure on the United States and worldwide, the primary objective of the vast majority of preclinical and clinical research in stem cell therapy for heart disease has been aimed at the recovery or regeneration of ischemic myocardium in adult patients. Less well studied, however, is the growing epidemic of pediatric heart failure. The causes of pediatric heart failure are not homogenous as mostly seen in adult heart failure but include multiple causes related to pressure and volume overload, dysrhythmias, and ischemia triggering ventricular dysfunction.1 On the basis of promising early results in adult patients, the application of stem cell therapy to patients with congenital heart disease (CHD) could potentially offer a new treatment paradigm. Research efforts to this end have been limited to a few number of relevant preclinical animal models and scattered clinical case reports. In this issue of Circulation Research, the Transcoronary Infusion of Cardiac Progenitor Cells in Patients with Single Ventricle Physiology (TICAP) trial, published by Ishigami et al2 represents an effort in the budding field of stem cell therapy for heart disease has aimed at the recovery or regeneration of ischemic myocardium in adult patients. Less well studied, however, is the growing epidemic of pediatric heart failure. The causes of pediatric heart failure are not homogenous as mostly seen in adult heart failure but include multiple causes related to pressure and volume overload, dysrhythmias, and ischemia triggering ventricular dysfunction.1

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Stem Cell Therapy For Patients With CHD

It is estimated that in the past decade >5000 patients worldwide have received some form of stem cell therapy for a variety of cardiovascular diseases. Among numerous stem cell types and formulations, 3 stem cell therapy candidates have emerged with promising results in early phase human clinical trials. Backed by a decade of preliminary work in large animal models, bone marrow–derived mesenchymal stem cells (MSCs) have shown safety, feasibility and preliminary efficacy to improve regional contractility, improve quality of life and decrease scar formation.3–5 MSCs have the capacity to self-replicate and differentiate into various tissue lineages. MSCs have unique immunologic properties because they have reduced expression of major histocompatibility complex (MHC) class-I molecule, and lack of MHC class-II molecule and costimulatory molecules CD80 (B7-1), CD86(B7-2), and CD40.6,7 Extensive results in preclinical animal models have shown that MSCs are immunoprivileged and have now been tested in phase I, double-blind randomized clinical trials as an allogeneic cell product. In the initial clinical trial, intravenous infusion of allogeneic MSCs were delivered to patients with an acute myocardial infarction.8 The results demonstrated that MSCs did not trigger an immune response and promoted improvements in pulmonary function, left ventricular (LV) function, and symptomatic global assessment with a decrease of cardiac arrhythmias. Subsequent to this encouraging trial, The Percutaneous Stem Cell Injection Delivery Effects on Neomyogenesis trial (POSEIDON) was a phase I/II randomized comparison of allogeneic and autologous MSCs in patients with chronic ischemic cardiomyopathy and showed that allogeneic MSCs were extremely safe and did not stimulate significant alloimmune reactions.9 Moreover, despite not being powered to show efficacy, both autologous and allogeneic MSCs injections reduced infarct size by ≈33%, reduced LV sphericity index, improved physical functional capacity, and improved quality of life. The exact mechanism of how MSCs perform their ability to recover myocardial function is still unknown, but may include differentiation into mature cardiomyocytes, decreased inflammation/scar formation, decreased cardiomyocyte apoptosis, secretion of paracrine factors, and stimulation of the resident c-kit+ cardiac stem cells (CSCs).

In parallel with advances in the application of bone marrow–derived mesenchymal cells has been the intense investigation of the therapeutic potential of c-kit+ resident CSCs and cardiosphere-derived cells (CDCs). The c-kit+ CSCs are defined by their multipotent, self-renewing, and clonogenic properties and have been clinically studied in the Cardiac Stem Cells in Patients With Ischemic Cardiomyopathy (SCIPIO) trial, which was reported as a randomized, open-label phase I trial in patients with ischemic heart disease and having undergone coronary bypass revascularization.9 The intracoronary delivery of c-kit+ CSCs was shown to be safe, with no serious adverse event reported. Despite not being powered to show efficacy, the treated patients with intracoronary delivery of the c-kit+ CSCs showed a reduction in myocardial scar formation and an increase in the LV ejection fraction (EF) by 12.3% during the first year of cellular transplantation over baseline, correlating with improved heart failure symptomology. Another cell type extensively studied is the CDCs, which are a heterogeneous population of CD105+/
CD45− mononuclear cells obtained from myocardial biopsies. The CardioSphere-Derived autologous stem cells to reverse ventricular dysfunction (CADUCEUS) trial was a prospective, randomized, phase Ib safety trial in adult patients with post–infarction LV dysfunction. The trial demonstrated that the CDC-treated patients had no reported arrhythmias, tumor formation, myocardial infarction, or other serious adverse cardiac events. Despite no improvements in cardiac function, there was significant reduction in scar mass, increased viable heart mass, regional contractility, and systolic wall thickening. With these encouraging results, a phase I to II trial using allogeneic CDCs rather than the autologous cells are being studied in adult ischemic patients.

Although the majority of research efforts have centered on applications for adult patients with ischemic heart disease, a few notable contributions have been directed at the progression of stem cell therapy as a treatment option for patients with CHD. In contrast to adult ischemic patients, CHD patients may have only one ventricle, which may become dysfunctional and, in some instances, involve a single right ventricle (RV). There have been limited preclinical CHD studies because there is no adequate animal model replicating all the salient features present in CHD patients. One study in a neonatal lamb model of acute RV pressure-overload demonstrated that intramyocardial injection of autologous umbilical cord blood stem cells significantly improved load-independent indices of systolic and diastolic functions in cell-treated versus placebo-treated lambs. Similarly, Hosashi et al showed in a rat model of RV pressure-overload that transplantation of skeletal myoblast sheets improved diastolic function, reduced RV fibrosis, and increased capillary density compared with controls. Experience in human pediatric patients, meanwhile, has been limited to case reports and small case series, with diluted cardiomyopathy the predominant disease type. Among these patients, LVEF improved 20% to 23% from baseline values in patients with diluted cardiomyopathy ranging from 4 months to 17 years of age. A similar benefit was observed in RV function after intracoronary delivery of bone marrow–derived progenitor cells to a patient with hypoplastic left heart syndrome (HLHS) in RV failure after a hybrid stage I procedure complicated by obstruction of the ductus arteriosus. Twelve months after stem cell administration, the systemic RVEF in this patient with HLHS improved from 22% to 44% and brain natriuretic peptide reduced from 2200 to 132 pg/mL. More recently, intraoperative administration of autologous umbilical cord blood stem cells was reported in a patient with HLHS during the stage II surgical palliation, where the RVEF improved from 30% to 35% before stage II to 50% at 3 months of follow-up.

TICAP Trial
HLHS is one of the most complex forms of CHD, with a reported incidence of 0.2 per 1000 live births or 0.9% of children born with CHD. Typically, patients with HLHS undergo 3-staged surgical procedures: stage I Norwood palliative operation in the neonatal period, stage II palliative bidirectional cavopulmonary connection operation at ≈4 months of age, and the stage III palliative total cavopulmonary connection (Fontan) operation at ≈3 years of age. Once a universally fatal diagnosis, dramatic improvements in staged surgical palliation have been achieved. Despite these strides in medical care, the mortality rate of these infants in the recent Single Ventricle Reconstruction (SVR) trial remained 25% to 35% during the first year of life. Although the cause of this attrition is multifactorial, clearly RV dysfunction plays an important role. In a report by Altmann et al, those patients who presented with depressed RV function had an 18-month survival of 35% compared with 70% for those with normal function. With cardiac transplantation remaining as the only alternative for patients with failing single ventricle circulations, there is a clear unmet need in patients with HLHS undergoing staged surgical palliation.

With the TICAP trial, Ishigami et al presented the first endeavor to offer a stem cell therapeutic to support the systemic RV of patients with HLHS. In this study, autologous CDCs were isolated, expanded, and administered via intracoronary delivery 4 to 5 weeks after the stage II palliative surgery or the stage III palliative surgery (Figure). No adverse events in the form of procedural complications, life-threatening dysrhythmia, myocardial necrosis, or sudden death were reported in the 7 patient CDC-treated cohort. At 18 months of follow-up, the CDC-treated patients demonstrated an improvement in RVEF from an average baseline value of 46.9±4.6% to 54.0±2.8% and a significant reduction in tricuspid valve annulus diameter, whereas control patients showed little improvement in RVEF, from 46.7±4.4% to 48.7±6.7%, and no change in diameter of the tricuspid valve annulus. CDC-treated patients also showed significant reductions in RV-free wall mass and indexed end-systolic and end-diastolic volumes at 18 months. Interestingly, the somatic growth of CDC-treated patients was significantly improved from baseline to 18 months, as indicated by an increase in z scores for height and weight, whereas there was no change in the control group. Similar to what has been shown in adult trials, CDCs continue to have an excellent safety profile in human trials.

Despite encouraging efficacy results, this study has many limitations that need further clarification to define the use of stem cell therapy in patients with HLHS. First, the design of the trial was not powered to show efficacy, even though the safety end point was achieved. Second, the treated patients with HLHS were heterogeneous with respect to their single ventricle physiology as treated patients could be after stage II or stage III palliative surgeries. Because the volume unloading of the HLHS heart may change with each operation, the functional cardiac improvements of the RV may not necessarily reflect the treatment of the CDCs, but instead indicate the natural remodeling that may occur in the RV over time. Third, there was no mechanistic insight into how the CDCs functioned in the RV. Finally, the enrollment of the patients with HLHS was not randomized and thus limited the interpretation of the study. However, despite these limitations, the results from this trial do not detract from the findings pertinent to the study’s main objectives, which were to evaluate the safety of autologous CDC injection to the RV of patients with HLHS.

Importantly, this trial represents several firsts in the realm of stem cell therapy for cardiovascular diseases. Not only is this the first completed stem cell trial in children with CHD but also it is the first attempt to deliver stem cells to a
univentricular heart. From a methodological point of view, this study reports the global delivery of cells to a nonischemic ventricle via intracoronary infusion of CDCs into coronary arteries having no atherosclerotic disease. Whereas previous clinical trials have used the stop-reflow technique for intracoronary delivery of cells to focal segments of ischemic or scarred myocardium,9,10 the TICAP trial required operators to engage and proximally occlude coronary blood flow to each of the major coronary arteries supplying a single ventricle heart 1 month out from surgical palliation. Using this technique, the authors reported no procedural complications and only transient ST-segment elevations during infusion. It should be noted, however, that patients were premedicated with amiodarone before intracoronary infusion, an important precaution that was not reported as necessary in other phase I CSC trials.9,10

**Future Focus**

**Translational Research**

The promise of stem cell therapy in patients with CHD is unique with a different set of challenges not seen in adults with ischemic heart disease. One of the key biological questions is the mechanism of action of stem cells in patients with CHD. We have shown that the main action of recovery of the CDCs derived from patients with CHD is the more potent cytokine release by the younger-derived CDCs when compared with adult-derived CDCs.20 This increased cytokine release by the younger-derived CDCs correlated with a stronger regenerative capacity in a rodent model of myocardial infarction and correlated with an increase in neoangiogenesis in the treated LV. We are now testing these younger-derived CDCs in other nonischemic ventricular dysfunctional rodent models, which may have more relevance to patients with CHD. Another important question is whether other stem cells have a similar regenerative capacity elicited by their cytokine release profile and how other stem cells’ regenerative capacities compare with CDCs when tested in animal models relevant to CHD. Other fundamental questions relevant to stem cell therapy in patients with CHD are the cell dosing, cell type, cell source (ie, allogeneic versus autologous), timing of intervention, frequency, and methodology of administration. For example, the TICAP trial administered autologous CDCs, whereas more recent evidence in rodent and swine models suggests that allogeneic CDCs are safe, equally effective,21,22 and now being studied in a trial for adult patients with ischemic heart disease.11 Finally, the indication of stem cell therapy for patients with HLHS remains to be defined, including whether a subset of patients with HLHS should be treated. For instance, maybe only patients with HLHS with RV dysfunction should receive stem cell treatment. The answers to these translational questions will be paramount to generate the best stem cell product to treat these challenging patients with CHD.

**Clinical Trials**

As a result of the successful completion of the TICAP trial, the same investigators are now recruiting patients for a phase II trial, the Cardiac Progenitor Cell Infusion to Treat Univentricular Heart Disease (PERSEUS) trial, which is a randomized trial aimed at assessing the efficacy of CDC therapy in patients with either single LV or RV lesions.14 Other ongoing or planned pediatric cardiac trials include phase I trials at Duke and Mayo Clinic,16 respectively. Both are designed to investigate the safety of autologous umbilical cord blood stem cell delivery to patients with HLHS. In addition, the Duke study will evaluate the efficacy of stem cell therapy to improve neurodevelopmental outcomes as a secondary outcome measure.14

Our institution will soon begin enrollment in a randomized phase I trial to administer allogeneic MSCs to patients with HLHS via intramyocardial injection at the time of the stage II palliative operation. MSCs have the advantage over other stem cells because of their longer proven safety record in adult clinical trials, which is paramount before being tested in patients with HLHS. Another unique property of MSCs is that their regenerative efficacy is unaltered as an allogeneic cell product, eliminating the many variables present in an autologous cell product.4 In addition to improvements in ventricular function, myocardial perfusion and reduction in scar size, a large animal study has shown that injected MSCs recruit and activate the endogenous pool of c-kit+ CSCs to areas of myocardial injury.23 This has

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**Figure.** Staged surgical palliation for patients with hypoplastic left heart syndrome. **A**, The stage I Norwood palliative operation; **B**, the stage II palliative bidirectional cavopulmonary connection operation; and **C**, the stage III palliative total cavopulmonary connection (Fontan) operation. Patients enrolled in the Transcoronary Infusion of Cardiac Progenitor Cells in Patients with Single Ventricle Physiology trial underwent intracoronary administration of cardiosphere-derived cells to each major coronary artery 4 to 5 weeks after the stage II or stage III procedure, as shown in **B** and **C**, respectively. IVC indicates inferior vena cava; LPA, left pulmonary artery; RA, right atrium; RPA, right pulmonary artery; RV, right ventricle; RVPA, right ventricle-pulmonary artery; and SVC, superior vena cava.
significant implications for the application of MSC therapy in children, in whom we have demonstrated an increased number of resident c-kit$^+$ CSCs in younger patients with CHD compared with adults.\textsuperscript{20} The timing of stem cell delivery during the stage II palliative operation in our trial was chosen for 3 main reasons. First, the high interstage mortality after the stage I operation, 12\% according to follow-up of 426 patients from the SVR trial, could mask the safety endpoints of a phase I study.\textsuperscript{21} Second, administration of MSCs at the stage II operation will allow the opportunity to study the effects of volume unloading on single RV systolic and diastolic function using cardiac magnetic resonance imaging, and evaluate whether the addition of MSC therapy shows improved RV function, not typically seen in patients with HLHS. Finally, a physiologically homogenous population of patients with HLHS would eliminate patient selection variables in the final analysis of the clinical results.

As the results of these early trials unfold during the next several years, the continuous exchange of successes, failures, challenges, and questions will be imperative to the successful translation of stem cell therapy for patients with CHD. The TICAP study is the first example of this interplay between breakthroughs in CSC biology and attention to the unmet clinical demands of complex patients with CHD. It is our hope that the positive TICAP preliminary findings will provoke initiation of similar clinical trials and continued translational research aimed at the advancement of stem cell therapy for patients with CHD.

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None.

References


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