Commentary: Stem cell therapy for single-ventricle congenital heart disease: Exciting, but a long way to go

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The diagnosis of a congenital heart defect necessitating single-ventricle (SV) palliation obligates a patient and family to a substantial commitment to their child's health. Palliation requires 3 operative interventions, and even then, the patient is left with a single functional ventricle. Because SV palliation was never designed to support both the systemic and pulmonary circulations, the eventual development of heart failure is an inevitability, a matter of time. Although many patients will survive well into adulthood before the development of heart failure, many will not.¹ As patients with SV circulations have heart failure develop, the only remaining treatment option is transplantation.²

Recently, stem cell therapy has been proposed to prevent the development of heart failure in patients with SV circulations. Although the mechanisms are unclear, they likely involve both the maturation of these cells into functional myocardium or endothelial cells and the activation of juxtacrine and paracrine mechanisms to improve angiogenesis and enhance cellular ability to mitigate oxidative stress.³

In this issue of the *Journal*, Sano and colleagues⁴ provide their expert opinion on the current state of cardiac stem cell therapy for pediatric patients. Sano and colleagues⁴ are to be congratulated not only for this excellent review but also for their many contributions to the field. The recent results of the TICAP (Transcatheter Infusion of Cardiac Progenitor Cells in Patients With Single-Ventricle Physiology) trial⁵ and the PERSEUS (Cardiac Progenitor Cell Infusion to Treat Univentricular Heart Disease) trial,⁶ in which these authors are involved, are encouraging. Initially, they demonstrated the safety of intracoronary stem cell injection of cardiosphere-derived cells, without an adverse event in either trial. In addition, they demonstrated improved ventricular function (higher ejection fraction and lower ventricular volumes), reduced heart failure (lower B-type natriuretic peptide and less fibrosis), increased weight for age, and improved quality of life.

Despite these findings, as is true for any potentially novel discovery, before stem cell use can become a more

clinically relevant treatment option, there remain many more questions than answers. What is the long-term effect on cardiac function? Will these patients need to be redosed? What type of stem cell will lead to the best results? How and when should the stem cells be harvested? How and when should they be administered? Will the impact of this therapy be more pronounced for patients with systolic or diastolic dysfunction? What is the overall mechanism, and how can we optimize it? Can stem cells be used as a rescue therapy? Many different studies performed in the course of many years will be necessary to answer this multitude of questions. A phase I/IIb randomized trial from the University of Maryland, the ELPIS (Longeveron Mesenchymal Stem Cells [LMSCs] Delivered During Stage II Surgery for Hypoplastic Left Heart Syndrome) trial, which uses bone marrow-derived mesenchymal stem cells injected intramyocardially during the time of the stage II operation, is currently underway.⁷ In addition, a study from the Mayo Clinic will use umbilical cord blood-derived stem cells administered intramyocardially at the time of the stage II operation.⁸

Current data do indicate that these strategies are safe, at least in the short-term. A lot, however, remains to be discovered before consistent clinical use. These successful short-term clinical trials will continue to push the field forward, provide enthusiasm, and lead to the continued evaluation of stem cell therapy in pediatric patients with SV palliation. Overall, the field is evolving rapidly, and it is very exciting.

Central Message

In the short term, stem cell therapy after single-ventricle palliation is safe and has promising outcomes. The long-term impact and optimal strategy, however, require many questions to be answered.

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