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EDITORIAL

The quest for a successful cell-based therapeutic approach for heart failure

Ana Marie Landin[1] and Joshua M. Hare[1,2]*

[1]Interdisciplinary Stem Cell Institute, University of Miami Miller School of Medicine, Miami, FL, USA; and [2]Department of Medicine, University of Miami Miller School of Medicine, Miami, FL, USA

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This editorial refers to 'Cardiopoietic cell therapy for advanced ischaemic heart failure: results at 39 weeks of the prospective, randomized, double-blind, sham-controlled CHART-1 clinical trial'†, by J. Bartunek *et al.*, on page 648.

Two-thirds of all heart failure is due to ischaemic heart disease.[1] These patients receive lifelong medication, experience significant morbidity and mortality, and often progress to heart transplantation or insertion of a left ventricular assist device,[1,2] In terms of population impact, a successful regenerative medicine strategy will have enormous impact upon patients with heart failure, who number in the millions worldwide. The staggering impact upon patients and healthcare systems provides extraordinary impetus for the development of a regenerative approach to treat these patients.[2,3] Indeed, the notion of affecting an improvement in left ventricular structure as a substrate for enhancing patients' quality of life and functional capacity (ultimately leading to reducing morbidity and mortality) is extraordinarily attractive.[2]

Cell-based therapy: the future for heart failure patients

This quest has spawned several clinical investigative efforts to devise an effective and efficient way to deliver cell-based therapy to this large patient population with major unmet needs.[4,5] This resulted in the testing of a vast array of cells (*Table 1*).[2] Currently, there are few decisive successes in the field. However, all of the current efforts are small, with no published studies exceeding 200 patients, and very importantly lack standardization. For reference, an early important study in the development of biventricular pacing enrolled 453 patients.[6]

The use of cardiopoietic stem cells in heart failure

In 2010, Behfar and colleagues demonstrated that mesenchymal stem cells (MSCs) could be guided to become cardiac progenitor cells in mice.[7] Furthermore, this study demonstrated that there are individuals that harbour stem cells with unique reparative capabilities, which are characterized by high expression of Nkx2.5, Tbx5, Mesp-1, and Mef2C and had unique cardio reparative properties [cardiopoietic stem cells (CpSCs)].[7] This study led to the design of a cardiac cocktail [transforming growth factor β1 (TGFβ1), bone morphogenetic protein 4 (BMP-4), Activin-A, retinoic acid, insulin-like growth factor-1 (IGF-1), fibroblast growth factor-2 (FGF-2), α-thrombin, and interleukin-6 (IL-6)] capable of guiding MSCs towards CpSCs.[7] This preclinical study formed the basis for a clinical trial: the C-CURE (Cardiopoietic Stem Cell Therapy in Heart Failure) trial which implemented CpSCs in humans with ischaemic cardiomyopathy,[8] demonstrating safety, as well as provisional efficacy including increased ejection fraction (EF), reduced left ventricular end-systolic volume (LVESV), and improved 6-min walk distance (6MWD) by cell therapy compared with standard of care.[8]

CHART-1 clinical trial

The C-CURE trial formed the basis for the CHART-1 trial, which is presented in the current issue of the journal.[9] CHART-1 (The Congestive Heart Failure Cardiopoietic Regenerative Therapy) is a double-blind, sham-controlled study in patients with ischaemic heart failure that randomized 315 subjects into treatment or sham procedure.[10] To date this is the largest trial of transendocardial stem cell injection (TESI) therapy in patients with ischaemic cardiomyopathy. Despite the promising results of C-CURE, the CHART-1 trial

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* Corresponding author. Interdisciplinary Stem Cell Institute, University of Miami Miller School of Medicine, Miami, FL 33136, USA. Tel: +1 305 243 5579, Fax: +1 305 243 5584, Email: JHare@med.miami.edu

Table 1 Cell types under investigation in cell-based therapy trials for heart failure

Cell types	Application
Unfractionated BM-MNCs	Ischaemic heart failure and chronic heart failure
$CD34^+$ stem cells	Chronic ischaemic failure
Mesenchymal precursor cells	Ischaemic heart failure
Adipose tissue derived MSCs	Ischaemic and non-ischaemic heart failure
Bone marrow-derived MSCs	Ischaemic and non-ischaemic heart failure
Cardiosphere-derived cells	Ischaemic heart failure
Cardiac c-Kit cells	Ischaemic heart failure
Cardiopoietic stem cells	Chronic heart failure
Induced pluripotent cell-derived cardiomyocytes	Chronic heart failure

BM-MNCs, bone marrow-derived mononuclear cells; MSCs, mesenchymal stem cells.

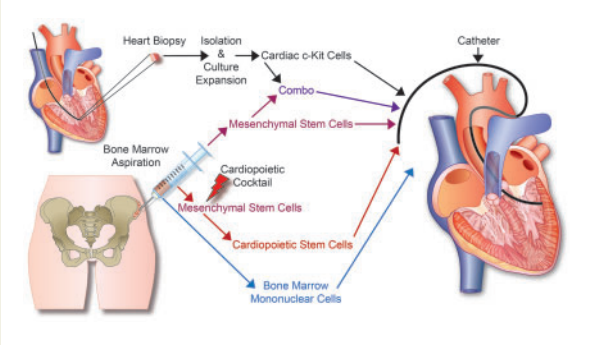

Figure 1 Stem cell therapy for heart failure: From tissue acquisition to stem cell expansion and delivery. Currently, autologous or allogeneic stems cells are derived from heart biopsies or bone marrow aspirations for various types of cell based therapies used in heart failure.

produced a negative result—no improvement was seen in the pre-specified composite endpoint relative to sham controls.

The primary endpoint utilized a Finkelstein–Schoenfeld hierarchical composite[8] that encompasses all-cause mortality, worsening heart failure, Minnesota Living with Heart Failure Score (MLHFS), 6-MWD, LVESV, and EF.[9] Of note, a subset of patients with ischaemic heart failure had favourable results provided that their left ventricular end-diastolic volume (LVEDV) was between 200 and 370 mL. In this subset of patients, an improvement in 6-MWD and reverse heart remodelling measured by LVESV were demonstrated. Although the overall results of this trial were neutral, the findings potentially form the basis for a larger study with a group of patients with greater LV remodelling.

Impact of negative clinical trials

Although negative studies can be disappointing, we learn and use them as a guide to help move a field forward. The first thing to be said is that negative clinical trials are far more common than positive ones, and have helped guide the field of heart failure therapeutics substantially over the past few decades. In fact, negative heart failure trials have assisted investigators in developing successful therapies and have helped greatly in modifying pathophysiological paradigms that form the basis for new therapeutic principles (e.g. targeting neurohormonal activation in heart failure).[11]

Factors for consideration

In the context of the CHART-1 results, it is valuable to take stock of the present state of the field, and consider some important factors regarding the state-of-the-art.

Cell preparations

There are multiple choices currently for cell preparation (*Table 1*), but almost no rigorous comparison studies. In order to identify the best therapeutic cells for each clinical application, there is a need for more direct cell comparison studies to be conducted in each specific heart condition. Several groups have conducted clinical trials with potentially promising results (*Figure 1*; *Table 1*). Despite promising early stage results, positive larger trials are lacking, with a notable exception in the Ixmyelocel-T trial.[12] An example of a cell comparison trial is the TAC-HFT trial, which suggested greater potency of MSCs compared with autologous whole bone marrow; arguably such a finding enhances the successful design of subsequent trials. To date, the CpSCs have not been directly compared with other MSCs in pre-clinical or clinical studies, nor have autologous vs. allogenic comparisons been conducted.

The quest to optimize cell potency is the underpinning of current trials that use cardiac stem cells or a combination of cardiac stem cells and MSCs in an attempt to enhance improvements in cardiac function, cell engraftment, and endogenous cardiac repair programmes,[13–16] which in turn could augment clinical outcomes.

Autologous vs. allogeneic

The issue of using allogeneic vs. autologous cell therapy requires further exploration. On first principles, an allogeneic cell source can be mass-produced in a quality-controlled fashion, whereas autologous preparations are more cumbersome and costly. Importantly, when using autologous therapy, each patient is receiving a unique cell-based drug. CHART-1 employed an autologous strategy; in this trial 12% of patients failed to expand their own bone marrow MSCs and could not be treated if randomized to the active group. Importantly, the underlying disease process could impair endogenous stem cell compartments as it has been shown that chronic inflammation such as occurs in heart failure patients can impair stem cells and potentially decrease their effectiveness.[17]

Pre-clinical testing

Limited testing of the cardiopoietic cell has been performed with only one animal trial in mice. Although rodents have served as a great model for generating valuable data in cardiovascular biology, there are significant differences between mice and humans that limit

extrapolation of results in to clinical trials.[18] It is important to emphasize that pre-clinical trials, particularly in large animals, are crucial to the success of clinical trials, allowing investigators to work out issues with dosing and delivery before getting to the clinical stage.[19] The CHART-1 study design could have been optimized potentially from additional large animal studies.

Dosing and delivery

A final and critical issue in the burgeoning field of cell-based therapy is dosing and delivery.[19] Several doses have been compared, from 20 to 200 million cells. Paradoxically, some studies indicate that lower doses or concentrations could yield superior phenotypic outcomes relative to higher doses.[4] In the case of the CHART-1 study, the target dose was 600 million cells.[10] An analysis of dose vs. outcome will be of great value.

The other point of importance is the route of delivery, i.e. intracoronary infusion, intramyocardial injection, or transendocardial injection. In the case of chronic heart failure, intracoronary infusion may not be the best route as underperfused regions would not be treated. In order to get the cells to the ischaemic regions, intramyocardial or transendocardial injections are of greatest effect. The CHART-1 investigators opted for intramyocardial injection in order to ensure delivery to the ischaemic regions.[10] Importantly, however, the CHART-1 study employed a unique injection catheter, not previously used in other clinical or pre-clinical studies.[9]

Conclusion

Although there is much to support enthusiasm for ongoing development efforts of cell-based therapeutics for heart failure, translation into positive late stage clinical trials with clinical efficacy has been a challenge. Here we have attempted to highlight some key areas of attention required for the field to advance, and have addressed issues of cell preparation, pre-clinical models, dose, and delivery for consideration. Important ongoing studies such as the CONCERT-HF (ClinicalTrials.gov Identifier: NCT02501811), BAMI [The Effect of Intracoronary Reinfusion of Bone Marrow-derived Mononuclear Cells (BM-MNC) on All Cause Mortality in Acute Myocardial Infarction (ClinicalTrials.gov Identifier: NCT01569178)], and DREAM-HF (ClinicalTrials.gov Identifier: NCT02032004) are underway which will further advance the field. While the CHART-1 trial produced a negative primary endpoint, this trial provides an important opportunity for the field to reappraise several critical issues that can enhance the success of future trials. Moreover, given the size of the trial, important hypothesis-generating subgroup analyses can be expected from the CHART-1 investigators that can further guide this field forward.

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