Changing of the guard?

James T. Willerson1*, Maria G. Cabreira-Hansen1, Doris A. Taylor2, and Emerson C. Perin1

1Stem Cell Center, Texas Heart Institute, Houston, TX; and 2Department of Regenerative Medicine Research, Texas Heart Institute, Houston, TX

This editorial refers to ‘Bone marrow-derived mesenchymal stromal cell treatment in patients with severe ischaemic heart failure: a randomized placebo-controlled trial (MSC-HF trial)†, by A.B. Mathiasen et al., on page 1744.

Cell therapy continues to hold promise as a future therapeutic modality for patients with heart failure. The first cells to be utilised in clinical trials in cardiovascular disease were autologous bone marrow-derived mononuclear cells (ABMMNCs).1 – 3 This was likely due to the fact that these cells are readily accessible and can be easily processed and given back to patients as an autologous fresh product in a short amount of time. In the absence of clinical experience, this was a good starting point. Over the next decade, important additional data were obtained with the use of ABMMNCs,4 – 6 and the initial positive results were tempered by negative results. Nonetheless, after much scrutiny, there seems to be a therapeutic signal,5 albeit a weak one. Overall, treated patients have shown relatively more robust results,13 a large phase 3 trial is currently underway to investigate the therapeutic role of these cells in heart failure patients (DREAM HF, NCT02032004). However, one must always be cautious as this is a very dynamic field, and another cell type, such as cardiac-derived stem cells or iPS cells, may take over as the best candidate after further development.

In addition to the progress in pursuing more potent single-cell therapies, it also seems possible that combinations of stem cells may be more effective than a single cell type alone. In a pre-clinical study, Williams and colleagues15 showed that the combination of cardiac resident c-kit cells and mesenchymal stem cells resulted in positive effects on left ventricular (LV) contractility in patients with ischemic cardiomyopathy and no other treatment options. Treated patients received a mean of 77.5 ± 67.9 x 10⁶ cells. The primary endpoint of their trial was a change in LV end-systolic volume (LVESV), as measured by magnetic resonance imaging or computed tomography at the 6-month follow-up. In this placebo-controlled, randomised trial comprising 55 patients (37 treated with MSCs and 18 treated with placebo), they found that LVESV decreased by 7.6 mL in the MSC-treated group and increased by 5.4 mL in the placebo-treated group. The difference between the 2 groups was 13.0 mL (P = 0.001). Compared to the placebo group, the treated group also showed a 6% increase in LV ejection fraction (P < 0.001), an 18 mL increase in stroke volume (P < 0.0001), and a 5.7 g increase in myocardial mass (P = 0.001). No significant differences were found in New York Heart Association classification, 6-minute walk time, or the Kansas City cardiomyopathy questionnaire.

These findings are in agreement with those from several previous clinical studies that also assessed the use of mesenchymal cells in similar patients.11 – 14 In these previous studies, allogeneic and autologous bone marrow-derived and adipose tissue-derived mesenchymal stem cells showed beneficial effects on various aspects of LV function and the occurrence of MACE in patients with ischemic cardiomyopathies and no other option for revascularization. Taken together, these newer studies represent a shift away from ABMMNC therapy. The mesenchymal cell has taken centre stage. Based on more robust results,13 a large phase 3 trial is currently underway to investigate the therapeutic role of these cells in heart failure patients (DREAM HF, NCT02032004). However, one must always be cautious as this is a very dynamic field, and another cell type, such as cardiac-derived stem cells or iPS cells, may take over as the best candidate after further development.

The therapeutic properties of mesenchymal stromal cells have been extensively investigated in a wide range of disease conditions (Figure 1).9 In this issue of the European Heart Journal, Dr Mathiasen and colleagues10 showed that transendocardial injections of autologous bone marrow-derived mesenchymal cells (MCS) resulted in positive effects on left ventricular (LV) contractility in patients with ischemic cardiomyopathy and no other treatment options. Treated patients received a mean of 77.5 ± 67.9 x 10⁶ cells. The primary endpoint of their trial was a change in LV end-systolic volume (LVESV), as measured by magnetic resonance imaging or computed tomography at the 6-month follow-up. In this placebo-controlled, randomised trial comprising 55 patients (37 treated with MCSs and 18 treated with placebo), they found that LVESV decreased by 7.6 mL in the MSC-treated group and increased by 5.4 mL in the placebo-treated group. The difference between the 2 groups was 13.0 mL (P = 0.001). Compared to the placebo group, the treated group also showed a 6% increase in LV ejection fraction (P < 0.001), an 18 mL increase in stroke volume (P < 0.0001), and a 5.7 g increase in myocardial mass (P = 0.001). No significant differences were found in New York Heart Association classification, 6-minute walk time, or the Kansas City cardiomyopathy questionnaire.

These findings are in agreement with those from several previous clinical studies that also assessed the use of mesenchymal cells in similar patients.11 – 14 In these previous studies, allogeneic and autologous bone marrow-derived and adipose tissue-derived mesenchymal stem cells showed beneficial effects on various aspects of LV function and the occurrence of MACE in patients with ischemic cardiomyopathies and no other option for revascularization. Taken together, these newer studies represent a shift away from ABMMNC therapy. The mesenchymal cell has taken centre stage. Based on more robust results,13 a large phase 3 trial is currently underway to investigate the therapeutic role of these cells in heart failure patients (DREAM HF, NCT02032004). However, one must always be cautious as this is a very dynamic field, and another cell type, such as cardiac-derived stem cells or iPS cells, may take over as the best candidate after further development.

In addition to the progress in pursuing more potent single-cell therapies, it also seems possible that combinations of stem cells may be more effective than a single cell type alone. In a pre-clinical study, Williams and colleagues15 showed that the combination of cardiac resident c-kit cells and mesenchymal cells administered transendocardially reduced infarct size and improved LV function more than either stem cell type alone in a porcine model of myocardial infarction. The Cardiovascular Cell Therapy Research Network will soon begin a clinical trial in the United States in which patients with ischemic cardiomyopathies will receive similar treatments (ie, mesenchymal cells, c-kit+ cells, or the 2 cell types in combination) (CONCERT-HF). This trial will help determine the potential benefits of combining mesenchymal and c-kit+ stem cells for treating patients with heart failure due to coronary heart disease and no other treatment options.
In summary, important progress has been made in the search for the ideal cell type, or combinations thereof, to obtain the best therapeutic effect for patients with heart failure. Mathiasen et al's positive results are an important addition to the current knowledge. We believe that mesenchymal cells represent a step in the right direction towards improving the therapeutic benefits of cell therapy in heart failure patients.

Acknowledgments
The authors would like to thank Heather Leibrecht, MS, and Marianne Mallia, ELS, of the Section of Scientific Publications at the Texas Heart Institute for their assistance in the editing of this manuscript.

Funding
Support was provided by the NHLBI’s Cardiovascular Cell Therapy Research Network.

Conflicts of interest: Dr Perin is a consultant for Mesoblast Ltd. Drs Willerson, Taylor, and Cabreira-Hansen have no conflicts to disclose.

References


A child with tumour thrombus extending to the right atrium

Jun Zeng, Jian-Qiao Zheng, and Hai Yu*

Department of Anesthesiology, West China Hospital, Sichuan University, 37# GuoXue Xiang, Chengdu 610041, China

* Corresponding author. Tel: +86 28 85423593, Email: yuhaishan117@yahoo.com

A 2-year-old girl presented with abdominal distention after 20 days of anorexia. Computed tomography revealed a 4.6 cm mass on the upper pole of left kidney with tumour thrombus extending from left renal vein to the right atrium. The transthoracic echocardiography demonstrated that inferior vena cava (IVC) was full of dense mass extending to the right atrium and obvious obstruction of blood flow (Panel A, Supplementary material online, Video S1). She underwent left radical nephrectomy, resection of the thrombus, and tricuspid valvuloplasty under mild hypothermia cardiaopulmonary bypass. Intraoperative transoesophageal echocardiogram revealed a 63 × 31 mm mass in the right atrium (Panels B and C). The freely moving mass prolapsed into the right ventricle in diastole and bouncing back in systole (Panel E, Supplementary material online, Video S2–S4). The enlarged left kidney (10 × 7 × 6 cm) was occupied by a large tumour, only litter tissue left in the lower pole. It is difficult to extract the tumour thrombus via right atrium intactly, so the suprarenal IVC incision/reconstruction was performed. The thrombus was divided into several sections and the largest one was 15 cm long (Panels D and F). Pathology confirmed Wilms tumour (WT) with negative lymph nodes margins. The patient recovered uneventfully and discharged 10 days later.

Supplementary material is available at European Heart Journal online.