

Cell Transplantation for Cardiac Repair

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Despite remarkable progress in contemporary cardiovascular therapy, treatment of heart failure still remains a therapeutic challenge. Pharmacological treatment using β -blockers, angiotensin converting enzyme inhibitors, and angiotensin-II receptor blockers, as well as surgical revascularization together with left ventricular reshaping procedures, has improved the quality of life for heart failure patients. At present, cardiac transplantation is the only radical treatment for end-stage heart failure patients who remain refractory to maximum conventional therapy, but the use of this technique is limited largely by organ shortage. There have been improvements in ventricular assist devices, and cardiac resynchronization has emerged as a promising treatment for patients with wide QRS complexes. However, most of these therapeutic options fail to address the fundamental cause of the problem, that is, compromised blood perfusion to the myocardium due to severe coronary atherosclerosis along with irreversible myocardial dysfunction and cell loss. Due to an inadequate intrinsic repair mechanism, the heart enters into a vicious cycle of left ventricular remodeling, characterized by progressive fibrosis and cellular degeneration. Thus, various cellular and molecular approaches that address these issues are currently generating a great deal of interest.^{1,2)} Of these, both therapeutic angiogenesis and stem cell-based therapy show encouraging results. Cell transplantation is based on the concept that stem cells with myogenic and/or angiogenic potential might compensate for cardiomyocyte loss and improve myocardial blood flow.

Stem cells of various origins and different potentials have been investigated. Autologous skeletal myoblasts were the first to undergo clinical trials.³⁾ Bone marrow derived stem cells have the potential to differentiate into bone, hematopoietic cells, myocardial, and endothelial cells. The heterogenous mononuclear fraction of the bone

marrow has the most promising stem cell populations, which have the potential to participate in the repair of diseased myocardium through transdifferentiation into heart muscle cells and to promote angiogenesis by secreting various angiogenic cytokines. Bone marrow derived endothelial progenitor cells play a significant role in the neovascularization of ischemic tissues. Various surface proteins have been identified for use in selection and enrichment of subpopulations of bone marrow cell transplantation studies. However, there is still no universal marker that can be used to identify bone marrow derived stem cells. Recent studies have suggested that ACC133, CD34, Lin- and c-kit could be important markers identifying subpopulations of bone marrow stem cells that would be useful for cardiac regeneration.

As a sole therapy for cell transplantation, Tse et al. implanted autologous bone marrow mononuclear cells in 8 patients with severe ischemic heart disease. Bone marrow cells were injected in the infarcted region using left ventricular electromechanical mapping with the NOGA system.⁴⁾ The three-month follow up revealed a significant reduction in the number of anginal episodes and improved left ventricular muscle wall thickness. Perin et al. reported a non-randomized phase-I study in 21 no-option patients having end-stage ischemic heart disease;⁵⁾ 14 patients received transendocardial injection of autologous bone marrow mononuclear cells using the NOGA electromechanical mapping system, and 7 patients served as controls. Four-month follow up showed a significant improvement in the contractile function of the segments where cells had been transplanted.

As an adjunct therapy, Hamano et al. injected autologous bone marrow mononuclear cells into the area of ischemic myocardium in 5 patients who underwent scheduled CABG.⁶⁾ One-year follow up revealed a significant improvement in regional perfusion and in overall cardiac function. Stamm et al. reported 12 patients who received intramyocardial cell transplantation as an adjunct to CABG.⁷⁾ The patients received the ACC133+ subpopulation of bone marrow mononuclear cells. Thallium-201 SPECT scan showed improved regional perfusion in the

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previously hypo- or non-perfused areas, although the centers of the akinetic infarct regions remained unchanged. There were no procedure-related complications, including arrhythmia or neoplasia, up to 14 months after treatment.

Cell transplantation for the treatment of patients with acute myocardial infarction has also been studied. An intracoronary cell delivery approach is less invasive and allows targeted delivery to the site of interest. Strauer et al. reported on the intracoronary delivery of bone marrow mononuclear cells in 10 acute myocardial infarction patients,⁸⁾ all of whom underwent percutaneous coronary interventions. Perfusion defects in treated patients decreased significantly, and there was improvement in the percentage of hypokinetic and akinetic segments of the left ventricle. Assmus et al. have reported the results of a randomized study, TOPCARE-AMI (transplantation of progenitor cells and regeneration enhancement in acute myocardial infarction) in which they carried out a comparison between bone marrow mononuclear cells and circulating progenitor cells for cardiac repair.⁹⁾ Transplantation of circulating progenitor cells was as effective as bone marrow mononuclear cells in improving contractile function of the heart and coronary artery flow reserve. Wollert et al. have reported the results of a randomized controlled clinical trial, BOOST (Bone marrow transfer to enhance ST-elevation infarct regeneration).¹⁰⁾ Sixty patients were randomized to receive optimum medical treatment and percutaneous coronary intervention with or without intracoronary CD34+ bone marrow cell transplantation. Six-month follow up using cardiac MRI showed that bone marrow cell transplantation improved left ventricular systolic function.

The beneficial cardiac repair effects of bone marrow stem cell transplantation have been assessed in controlled phase-I clinical studies, which have suggested the safety and feasibility of this approach and have shown a restoration of left ventricular wall thickness, an improvement in mechanical contractile function in the area of cell engraftment, enhanced regional blood flow, and overall improvement in global cardiac function. Despite these encouraging results, the demographic and clinical characteristics of the patients in these studies have been quite variable, making it difficult to conclusively show the beneficial effects of bone marrow cell transplantation. Most of the studies lack a true placebo arm and blinded evaluation of the results. Moreover, there is a lack of data to help explain the mechanistic basis of the beneficial effects on cardiac function of cell therapy. Some of the stud-

ies have associated the improvement in cardiac function with the restoration of left ventricular wall thickness, which leads to improved regional contractility. This is hypothesized to result from the transdifferentiation of the transplanted cells into cardiomyocytes or neoangiogenesis that leads to improved regional blood flow in the ischemic area.

With respect to cell delivery, systemic administration may not be feasible, as it may spread the cells to undesired tissues and organs. Thus, the targeted delivery of cells to the areas of interest presents the ideal approach for achieving the desired benefits of cell transplantation. Intracoronary administration may be more practical, and possibly may result in the global dissemination of the cells in the myocardium. However, a recent study in a canine model of myocardial ischemia has shown that micro-infarction developed when bone marrow mesenchymal stem cells were delivered by the intracoronary route. Intramyocardial administration has been widely adopted for cell transplantation in both pre-clinical and clinical studies. However, surgical delivery is limited to patients who require surgical intervention. Transendocardial delivery with the electromechanical mapping NOGA system has been used in clinical studies. As an alternative to these delivery approaches, bone marrow stem cell mobilization using an arbitrarily selected cytokine is gaining popularity in clinical studies. However, cytokine therapy has associated side effects for which patients should be carefully monitored. An important aspect of transplantation is defining the patient population that can benefit from cell therapy. As well, age-related decreases in proliferative potential and differentiation potential of bone marrow stem cells need to be considered.

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