Cardiac stem cell therapy research in China

Junbo GE

Center of Stem Cell and Tissue Engineering, Shanghai Institute of Cardiovascular Disease, Zhongshan Hospital, Fudan University, Shanghai 200032, China

For more than two decades, the morbidity and mortality of coronary artery disease (CAD) has been increasing rapidly in China. Despite tremendous advances in treatment strategies of CAD, heart failure after acute myocardial infarction (AMI) continues to be one of the greatest medical challenges throughout the world. In 1994, Soonpaa and colleagues first reported the possibility of cardiomyocytes implantation and suggested that intracardiac cell grafting might provide a useful approach for myocardial repair.\(^1\) Cell implantation has become a novel therapeutic option for ischemic cardiac injury and heart failure.

Stem cells are defined as cells that have clonogenic and self-renewing capabilities and that differentiate into multiple cell lineages. Whereas embryonic stem cells are derived from mammalian embryos in the blastocyst stage and have the ability to generate any terminally differentiated cell in the body, adult stem cells are part of tissue-specific cells of the postnatal organism into which they are committed to differentiate. Early researches suggested that implanted adult stem cells, when under local microenvironment, be induced to transdifferentiate into tissue-specific cells, such as cardiomyocyte, endothelial cell, and smooth muscle cell, that is, they have so called developmental plasticity.\(^2\) Subsequent studies have challenged this concept. In 2004, two independent groups reported in Nature that transplanted bone marrow stem cells (BMCs) could not differentiate into cardiac myocytes but different blood cells.\(^3,4\) However, in 2005, Kajstura et al. demonstrated that BMCs, when properly administrated in the infarcted heart, efficiently differentiate into myocytes and coronary vessels with no detectable differentiation into hemopoietic lineages, independently of cell fusion.\(^5\) In spite of the uncertainty and controversy regarding the underlying mechanism by which stem cell transplantation and differentiation lead to cardiac repair, the first clinical study on cardiac stem cell transplantation was initiated in 2001. Thereafter, several clinical studies, such as the TOPCARE-AMI trial in 2002\(^6\) and BOOST\(^7\) in 2004, demonstrated that intracoronary infusion of progenitor cells is feasible and may improve the recovery of left ventricular contractility in patients with acute myocardial infarction. More recently, several clinical trials of stem cells mobilized by granulocyte-colony stimulating factor (G-CSF) after myocardial infarction have indicated that G-CSF treatment is safe and may improve left ventricular function.\(^8\) Now it is generally considered that stem cells transplantation may improve functional recovery of infarcted or failing myocardium by various potential mechanisms, including direct or indirect improvement of neovascularization. Paracrine factors released by progenitor cells may inhibit cardiac apoptosis, affect remodeling, or enhance endogenous repair, while differentiation into cardiomyocytes may contribute relatively less to cardiac regeneration.\(^9\)

In recent years, many basic researches and clinical studies on cardiac cell therapy have been carried out throughout China. In 2005, many of China’s most prominent research groups had presented their research results at the Shanghai Stem Cell Symposium, an international meeting focused on cardiac stem cell research and sponsored by the Chinese Medical Association. Stem Cell Transplantation for the Treatment of Coronary Artery Disease and Heart Failure is a randomized, prospective, multi-center clinical trial sponsored by grants from the Ministry of Science and Technology as a national key scientific program. This study, which was designed to recruit 500 patients admitted to several major medical centers in China and a follow-up period of 2 years, has initiated in 2003. Until the end of 2005, more than 600 patients have been recruited. In one randomized, controlled and prospective study, Ge et al. evaluated the efficacy and safety of intracoronary transplantation of autologous mononuclear bone marrow cells for the treatment of patients with ST-segment elevated acute anterior myocardial infarction (MI), sub-acute anterior MI, old anterior MI and idiopathic dilated cardiomyopathy (IDC). Patients were followed up for 6 months. The results showed that transplantation of BMCs resulted in significant improvement of cardiac function in patients with acute and sub-acute MI, but had limited effects on patients with old MI and IDC.\(^10,11\) In another study

Corresponding author: Dr. Junbo GE, Shanghai Institute of Cardiovascular Disease, Zhongshan Hospital, Fudan University, Shanghai 200032, China. E-mail: junboge@zhospital.com
reported by Li and colleagues, patients with AMI received either intracoronary transplantation of G-CSF mobilized autologous peripheral blood stem cells (PBSCs) in addition to standard therapy (including drug therapy and percutaneous coronary intervention) or standard therapy alone. Their results showed that G-CSF mobilized autologous intracoronary PBSCs transplantation is a safe and feasible treatment for patients with AMI and global left ventricular function is improved and left ventricular remodeling attenuated at 6-month follow-up.\(^{12}\) Wang et al.\(^{13}\) also found that percutaneous coronary autologous mesenchymal stem cells (MSCs) transplantation have no significant short-term effect on cardiac function in patients with IDC. Cao et al. also reported their small-sample study on MSCs transplantation for the treatment of patients with CAD or chronic heart failure, with similar results.

Several other studies on cardiac stem cell therapy are also ongoing in China. Researchers from Fuhui Hospital in Beijing found that both intracoronary transplantations of autologous mononuclear bone marrow cells or endothelial progenitor cells (EPCs) are effective in improving cardiac function and reducing ischemic-reperfusion injury in animal models, and EPCs showed better efficacy and safety. Some researchers in China are investigating stem cell transplantation for the treatment of cardiac arrhythmias.

Although stem cell is a promising therapeutic modality for patients with significant cardiac dysfunctions, there are still many questions to be addressed before its clinical application. First, which type (or types) of cell should be used? Second, when is the optimal time for cell transplantation? Third, an ideal method for cell delivery is yet to be found. We know that BMSCs transplantation is not absolutely safe, and skeletal myoblasts and hematopoietic stem cells are associated with proarrhythmic effects and potential tumor formation. Recent studies raise the concern of increased in-stent restenosis after G-CSF mobilization. Vulliet et al. found that administration of MSCs by intracoronary injection was associated with occlusion of microvessels and macrovessels.\(^{14}\) In a study with rat model, Yoon et al. found that direct transplantation of unselected bone marrow cells into the acutely infarcted myocardium may induce significant intramyocardial calcification.\(^ {15}\) Rubio and colleagues showed that human MSCs can undergo spontaneous transformation following long-term in vitro culture.\(^ {16}\)

What should be emphasized is that at present, stem cell is far from an established treatment for cardiovascular disease but an approach under investigation. We should be more cautious to choose the study subjects. There is still no generally accepted protocol for the cardiac stem cell research in China. Also, there are some problems regarding the practice, e.g., randomization and controls should be stricter in clinical trials; stem cells should be isolated according to more precise procedures; investigators of cardiac stem cells should work more closely with the qualified interventional cardiologists.

Cardiac stem cell techniques are undergoing translation from laboratory research to clinical application. Whatever the underlying mechanisms are, both animal study and clinical trials have provided evidence for the efficacy for stem cell transplantation to improve cardiac function. Despite the problems we are facing, stem cell transplantation remains a highly promising therapeutic strategy for the treatment of cardiovascular disease and holds great potential for the future. Given our growing understanding of the cell differentiation, signal transduction, molecular mechanism of cell homing, and more knowledge we get from multicenter, double-blind, randomized, controlled clinical trials, the time will come when stem cell therapy becomes a treatment of choice for patients with cardiac dysfunction.

**References**

11. Huang RC, Yao K, Ge JB, et al. Long term follow-up on emer-


