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Review Article

Stem cells in clinical practice for cardiovascular diseases

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ABSTRACT

Introduction: According to a World Health Organization (WHO) report, 17.3 million people died from cardiovascular diseases (CVDs) in 2008, representing 30% of all global deaths, and almost 23.6 million people will die from CVDs by 2030. CVDs remain the predominant cause of mortality worldwide.
Aim: In this review, the authors discuss the current strategies and therapies targeting stem cells in CVDs.
Material and methods: In this paper we present an overview of stem cell therapy for CVD and discuss the challenges these three areas present for maximum optimization of the efficacy of stem cell therapy for heart disease, and new strategies in progress.
Discussion: Various kinds of therapeutic methods have been studied to improve prognosis in cardiovascular diseases. Stem cells comprise an enormous opportunity to rebuild damaged tissues. Most of the application and clinical trials involve the various types of stem cells derived mainly from bone marrow and others sources of mesenchymal stem cells. Early data from these trials have produced mixed results often showing minor or transitory improvements.
Conclusions: The divergences are attributed to differences in cell preparations, the large number of stem cell types under investigation in different clinical settings, timing, methods of cell administration and characteristics of patients.

1. Introduction

According to a World Health Organization (WHO) report, 17.3 million people died from cardiovascular diseases (CVDs) in 2008, representing 30% of all global deaths, and almost 23.6 million people will die from CVDs by 2030.[1] Although many drugs and medical devices have been developed, the incidence of CVDs remains high. The field of cardiac cell therapy has emerged as a new alternative in this situation, and has made

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rapid progress. The use of stem cells to improve recovery of the injured heart is an important emerging therapeutic strategy.

Stem cells comprise an enormous opportunity to rebuild damaged tissues. To understand their functions, physiology and action, cells are tested not only *in vitro* but also *in vivo* in animal models. Stem cell therapy induces both therapeutic and side effects; therefore, extensive evaluation of the side effects is needed to decide if a treatment can be adopted in medical practice. Stem cell transplantation in human patients must ensure safety and therapeutic efficacy. Preclinical studies with animal models provide strong evidence for obtaining a relevant positive clinical outcome.

The main challenges of stem cell therapy for CVD are improved identification, recruitment, and expansion of autologous stem cells; the identification of mobilizing and homing agents that increase recruitment; and developmental strategies to improve stem cell survival during the engraftment of both endogenous and exogenous sources of stem cells.[2] During the past decade, multiple candidate cells have been proposed for cardiac regeneration. Moreover, the first clinical trials with cell-based therapies have been performed. At present, it is believed that stem cell therapy could lead to cardiac regeneration in various ways – differentiation of the administered cells into all of the cellular constituents of the heart, the release of paracrine factors, the stimulation of endogenous repair by injected cells, or a combination of these mechanisms.[3] The most likely route of action seems to be the paracrine influence, where the effectiveness of stem cells is related to the secretion of soluble factors that contribute to cardiac repair and regeneration. Moreover, cytokines and growth factors can induce cytoprotection and neovascularization. Additionally, as stem cells are released in a temporal and spatial manner, they exert various effects depending on the microenvironment after injury and may have an autocrine impact on the biology of stem cells themselves. Moreover, these stem cells may influence adjacent cells and exert their actions *via* several mechanisms.[3]

A myocardial infarction (MI) is the ischemic necrosis of the cardiac tissue and it is frequently triggered by severe coronary stenosis. The decrease in myocytes produces abnormal left ventricular (LV) remodeling, chamber dilatation and contractile dysfunction.[4] In patients after MI delivering naturally myogenic cells (i.e., skeletal myoblasts, cardiomyocytes, or any progenitor cell driven down a muscle lineage) seems to be a high priority. However, the formation of new myocardium has been established for embryonic stem cells (ESCs). In turn, bone marrow (BM) mononuclear cells (BMMCs) are an easily accessible source of adult stem cells. For patients with chronic ischemia, application cells with angiogenic potential, such as BMMCs, endothelial progenitor cells (EPCs), vascular progenitor cells or mesenchymal stem cells (MSCs), seem to have more therapeutic potential.

2. Aim

In this paper we present an overview of stem cell therapy for CVD and discuss the challenges these three areas present for maximum optimization of the efficacy of stem cell therapy for heart disease, and new strategies in progress. We also discuss important questions that remain to be investigated to ascertain a successful translation of current experimental knowledge regarding cell therapy for myocardial repair/replacement.

3. Material and methods

3.1. Stem cells in clinical study

3.1.1. The bone marrow as a source of cardiogenic cells

The inflammatory process after myocardial ischemia stimulates the recruitment and homing to the cardiac the endogenous BM derived cells (BMDCs). It is connected with the mobilization a number of cytokines.[4,5] Preclinical studies of cell-based therapy with BMDCs showed impressive regeneration of lost myocarium, improvement of cardiac function and formation of new capillaries in both small and large animal models.[6] There are some early reports that BMDCs may transdifferentiate into skeletal muscle, hepatocytes or cardiomyocytes.[7,8] However, it is not completely known if improved cardiac function after therapy with those cells was caused by the paracrine theory of cardiac protection and regeneration. This paracrine action includes secretion of cardioprotective cytokines, angiogenic factors or factors which activate resident cardiac stem cells.[9]

After successful preclinical studies in animal models, the rapid transition to the clinical use of BMDCs took place. A significant contribution is the fact that BM can be easy accessed, is renewable, and contains a mixture of autologous cells with regenerative capacity. Much attention has been paid to the mononuclear cell fraction, mainly due to the full array of hematopoietic stem cells, MSCs, EPCs and side population cells. All of these cell types were shown to improve cardiac function if transplanted into infarcted myocardium in various animal studies.[6,10–13]

The first human clinical trial with stem cells in an acute myocardial infarction (AMI) patient was done using an intracoronary infusion of autologous BM unfractionated mononuclear cells. At 10 weeks after the stem cell transplantation, the infarct area had been reduced from 24.6% to 15.7% of LV circumference, while the ejection fraction, cardiac index and stroke volume had increased by 20%–30%.[14]

Several randomized trials showed measurable improvements that were comparable to established therapeutic regimes. Nonrandomized, smaller-scale trials also produced variable results, ranging from no significant changes in LV ejection fraction (LVEF) to a significant improvement. The meta-analysis of 18 randomized and non-randomized trials involving AMI and chronic ischemic cardiomyopathy patients found that transplantation of BMDSCs improved the LVEF by 5.40%, decreased infarct scar size by 5.49%, and lowered LV end-systolic volume by 4.80 mL.[15]

Application of BMMCs caused improved LV contractility in the infarct border zone and global LVEF by 6% in the BOOST trial,[16] 2.8% in the REPIR-AMI trial,[17] 5% in the FINCELL trial,[18] and 3% in the REGENT trial.[19] A high volume of this factor was obtained in a non-randomized trial undertaken by Srimahachota and co-workers[20] – 7%. By contrast, in the ASTAMI trial[21] no significant effects on LVEF, LV volumes, or infarct size were