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EXPERT OPINION

Bone marrow cell therapies in ischemic cardiomyopathy

Marcin Wysoczynski, Kyung U Hong & Joseph B Moore IV†
University of Louisville, Institute of Molecular Cardiology, Department of Medicine, Louisville, KY, USA

Decrements in ventricular function due to the permanent loss of contractile tissue remain problematic in patients with ischemic cardiomyopathy. For this reason, cell replacement therapy has received much popularity in recent years. Bone marrow is an abundant and accessible source of stem cells with regenerative potential. However, ischemic heart disease clinical trials based on bone marrow-derived stem cell (BMC) infusion have yielded discrepant results and marginal therapeutic benefits, making this modality's future uncertain. Further investigation of molecular and cellular characteristics critical for therapeutic efficacy and defining the mechanism(s) of BMC-mediated cardiac repair will be paramount for harnessing their full therapeutic potential.

Keywords: acute myocardial infarction, bone marrow, cardiac regeneration, cell therapies, chronic heart failure, ischemic cardiomyopathy

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1. Introduction

Reduction of detrimental remodeling and improvement of cardiac function in patients with ischemic cardiomyopathy remains an unmet challenge in the field of cardiovascular medicine. Despite the employment of numerous pharmacological and surgical interventions, acute ischemic events often result in ongoing ventricular myocardial attrition and ensuing congestive heart failure (HF) not amenable to current therapeutic modalities. With common treatment strategies failing to address the underlying pathophysiology of cardiac dysfunction following ischemic injury, such as left ventricular (LV) dilation and remodeling due to cardiomyocyte death and fibrosis, cell-based regenerative therapies have gained momentum in the clinical realm. Such strategies aim to ameliorate cardiac function and abrogate ventricular remodeling through replacement of lost or impaired cardiomyocytes, promotion of revascularization and inhibition of fibrosis. Within the past decade, identifying sources of adult stem and progenitor cells with cardiogenic potential have been a high priority topic of investigation. Early landmark studies, ~ 13 years ago, demonstrating that transplanted BMCs were capable of reconstituting infarcted myocardium in ischemic animal models [1] attracted widespread enthusiasm regarding the prospective therapeutic utility of such cells for the treatment of ischemic cardiomyopathy. These initial observations rapidly paved the way for numerous innovative clinical trials investigating the safety, feasibility, and therapeutic efficacy of BMC administration to patients with ischemic heart disease (IHD) [2]. Despite promising results obtained from preclinical investigations, clinical trials assessing the ability of bone marrow-derived stem cells (BMCs) to improve cardiac functional parameters in patients with ischemic disease have yielded variable results [2,3] leaving their future as a viable therapeutic option uncertain. Here the development, current status and future outlook of BMCs for the treatment of acute myocardial infarction (MI) are discussed.

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2. Bone marrow cells: an extracardiac origin for cardiogenic cells

It has nearly been over a decade since the erosion of a widely accepted dogma that the human heart is a post-mitotic organ lacking intrinsic regenerative and repair capabilities. This began with early reports that demonstrated cardiac myocytes to actively proliferate in end-stage HF [4] and after MI [5]. Not soon after, it was suggested that the heart's regenerative capacity, albeit ostensibly physiologically insignificant, was not restricted to resident populations but may also receive contributions from remote and circulating stem cells of extracardiac origin. The most compelling evidence of this was acquired from clinical investigations in which patients underwent sex-mismatched orthotopic heart transplantation. In these studies, male patients received hearts from female donors and subsequent levels of chimerism were enumerated via fluorescence *in situ* hybridization-mediated detection of the male Y chromosome [6,7]. Several months post transplantation, fluorescence microscopy revealed a mixed level of host cardiomyocyte chimerism ranging from 0.04 [7] to 9.0% [6]. Notwithstanding the varying degrees of chimerism reported, primitive cells derived from the recipients were shown to have actively repopulated the grafted heart wherein they gave rise to discrete Y chromosome-positive cell populations that included cardiac myocytes, smooth muscle and endothelial cells. Such studies suggested that the human heart possesses extracardiac progenitors with proclivity to home and reconstitute damaged myocardium. At that time, little information was known regarding the exact origin of these cardiogenic cells. However, in light of more recent reports demonstrating the regenerative capacity of hematopoietic BMCs in murine coronary ligation [1] and rat cryoinjury [8] infarct models, increasing attention was brought to the bone marrow as the potential source. In support of this, a reservoir of tissue committed stem cells within adult bone marrow expressing markers for cardiac differentiation has been discovered [9]. These cells, which reside in the non-hematopoietic mononuclear cell fraction of adult bone marrow, are actively mobilized into peripheral blood on cardiac injury. Moreover, previous clinical studies demonstrated the magnitude of acute bone marrow stem/progenitor cell mobilization to positively correlate with long-term improvement of ejection fraction in patients 1 year after MI [10], suggesting that mobilization of non-hematopoietic BMCs following injury may serve as an intrinsic mechanism for cardiac repair. Results from these and other preclinical studies sparked excitement regarding their prospective use for cell-based regenerative therapies and laid the groundwork for several clinical trials investigating the safety and efficacy of BMCs for the treatment of cardiac ischemic injury.

3. BMC therapy for ischemic heart disease

In a recent meta-analysis, the clinical impacts of BMC transplantation in patients with IHD was comprehensively reviewed [2]. The study compiled and systematically evaluated the clinical outcomes of 50 datasets. These included 36 randomized controlled studies and 14 cohort studies that encompassed 2625 enrolled patients with either acute MI or chronic IHD. Clinical end points assessed included alterations in LV ejection fraction, LV end-systolic volume, LV end-diastolic volume and infarct size. Irrespective of study design (i.e., route of injection, number of cells administered, various BMC populations and cardiac imaging modality) and type of IHD, BMC-treated patients exhibited modest yet statistically significant improvements in both ventricular cardiac function and clinical outcomes. On average, patients which received BMCs had a 3.96% increase in LV ejection fraction and ~ 4.03% reduction in infarct size. Further, BMC-treated patients also exhibited decreased LV end-diastolic (≈ -5.23 ml) and end-systolic volumes (≈ -8.91 ml). Thus, data from the largest meta-analysis to date significantly support the notion that BMC transplantation improves ventricular function and detrimental post-infarct remodeling [2]. However, with an impending clinical trial came further discrepancies regarding the feasibility of this therapeutic approach. For instance, in the Swiss-AMI trial (NCT00355186) [11], published in 2013, intracoronary administration of bone marrow-derived mononuclear cells (BM-MNCs) did not improve LV ejection fraction whether cells were injected at 5 – 7 days or 3 – 4 weeks after the MI event. This lack of ventricular improvement with BM-MNC treatment was paralleled in a more recent meta-analysis [3]. In this study, combined results from 22 randomized AMI control trials demonstrated statistically significant improvements in LV ejection fractions (+ 2.10%), LV end-systolic (-4.05 ml) and LV end-diastolic (-2.80 ml) volumes and infarct sizes (-2.69%). However, no improvement in major adverse cardiac events was detected after a 6-month median follow up nor was an effect observed on cardiac function, volumes or infarct size in a subset of trials that employed cardiac MRI-derived end points. Numerous factors could be acknowledged in effort to resolve the disparities presented in these clinical trials; however, the most plausible would include variable methods of BMC isolation and expansion techniques which could have pronounced effects on their *in vitro* cellular characteristics. Further, such differences would have consequences on what may be the foundation of a successful clinical trial – that is the efficient homing, engraftment, and robust differentiation of infused BMCs at the site of cardiac injury.

This principle was followed in the CELLWAVE (NCT00326989) [12] and C-CURE (NCT00810238) [13] clinical trials. For example, based on a previous report which demonstrated focused low-energy shockwaves to boost the expression of chemoattractants in target tissues [14], the CELLWAVE trial used cardiac shockwave pretreatment to enhance the homing efficiency and reparative potential of intracoronary delivered BM-MNCs in patients with chronic HF. In this trial, shockwave-assisted administration of BM-MNCs resulted in a statistically significant yet modest improvement in LV ejection fraction, as well as a decreased incidence of adverse cardiac

events relative to shockwave treatment alone [12]. Further, with the C-CURE clinical trial, bone marrow-derived mesenchymal stem cells (BM-MSCs) were stimulated *in vitro* to express cardiac-lineage commitment markers prior to injection. This approach was developed to enhance their cardiomyogenic potential or rather their proclivity to differentiate into mature cardiac cellular lineages following intramyocardial infusion in patients with chronic HF. Six months following treatment, lineage-guided MSC-treated patients exhibited improved LV ejection fractions (≈ 7%), decreased LV end-systolic volumes (≈ -16 ml) and advanced composite clinical scores relative to patients who received standard of care alone. Currently, these studies are being followed up with an approved Phase III clinical trial, CHART-1 (NCT01768702), investigating the safety and efficacy of lineage-guided (cardiopoietic) BM-MSCs in patients with chronic HF. The CELLWAVE and C-CURE clinical trials utilized previously established preclinical methodologies to enhance the therapeutic efficacy of administered BMCs by exploiting cell characteristics that influence their regenerative properties, such as cell homing [14] or cardiomyogenic differentiation potential [15], respectively. Although cardiac functional improvements were modest in these studies, they are representative of a progressing field which seeks to exploit amenable molecular pathways underlying BMC characteristics to enhance their suitability for cardiac regenerative applications.

The underlying mechanisms of BMC-mediated cardiac repair are still unclear. Preceding reports initially suggested that BMC transplantation contribute to regeneration via direct differentiation into cardiac-specific cell lineages [1]. However, a more recent consensus points to mechanisms of an indirect nature, wherein secretion of paracrine factors by donor cells may facilitate the activation of endogenous repair mechanisms.

4. Expert opinion: future perspectives on BMCs for the treatment of ischemic cardiomyopathy

Despite numerous animal studies and clinical investigations exploring the cardiac reparative potential of BMCs, the true therapeutic benefits imparted by adult BMC administration to patients with cardiac ischemic injury remains contentious. Indeed, the relative ease of isolation and abundance of BMCs in either a patient's bone marrow or peripheral blood makes for an attractive cell product for therapeutic applications, but procedural imperfections for processing and isolation may impact their regenerative characteristics – and may well have contributed to inconsistencies observed in some previous clinical trials [2,3]. Currently, a consensus view concerning the therapeutic efficacy of BMC transplantation has not been reached and may directly relate to trial results that are befuddled by an exorbitant number of variables. These include differing classes of BMCs, routes of administration, cell injection numbers, study designs (cohort vs randomized), patient selection criteria and modalities of cardiac imaging utilized in various stem cell trials.

Regardless of some conflicting reports and the often lackluster improvements in ventricular function observed with BMC transplantation [2,3], results from > 50 clinical studies proffer some support regarding their ability to improve long-term survival and ameliorate adverse outcomes in patients with ischemic cardiac injury. Thus, it is our view that BMC therapy has potential to become a viable treatment option. However, unsophisticated isolation and expansion techniques, as well as a considerable lack of knowledge regarding BMC-mediated mechanisms of cardiac repair have hindered and continue to hinder their clinical progress. Consequently, effort must be placed on the identification of BMC genetic and molecular pathways that modulate stem cell characteristics which support engraftment, proliferation and differentiation into cardiac parenchyma (e.g., cardiomyocyte, endothelial and vascular smooth muscle cell lineages). These BMC features are crucial for the reconstitution of damaged myocardium and restoration of ventricular performance. Such philosophies have been followed in more recent clinical trials in an attempt to enhance the therapeutic efficacy of BMCs through enhancement of cell retention [12] and promotion of cardiac lineage differentiation [13]. Such studies provide direction and insight concerning the numerous avenues that must and have yet to be explored in an effort to unlock the full regenerative and clinical potential of BMCs.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending or royalties.

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Affiliation

Marcin Wysoczynski[1] PhD,
Kyung U Hong[1] PhD &
Joseph B Moore IV[†2] PhD
[†]Author for correspondence
[1]Assistant Professor of Medicine,
University of Louisville, Institute of Molecular Cardiology, Department of Medicine,
Louisville, KY, USA
[2]Assistant Professor of Medicine,
University of Louisville, Institute of Molecular Cardiology, Department of Medicine,
580 S. Preston St., Baxter II, Rm 119D,
Louisville, KY, USA
Tel: +1 502 852 2036;
Fax: +1 502 852 2484;
E-mail: jbmoor01@louisville.edu