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STEM CELLS Bone-marrow-derived cells and heart failure—the debate goes on

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Abstract

The therapeutic efficacy of bone-marrow-derived cells in patients with acute or chronic myocardial infarction has been a matter of intense debate. Three new clinical trials—the Swiss-AMI, CELLWAVE, and C-CURE studies—unfortunately do not resolve the controversy in the field of cell therapy for the damaged heart.

The results of three clinical trials of stem cell therapy, conducted in patients with acute myocardial infarction (AMI)¹ or chronic heart failure (HF) of ischaemic origin,^{2,3} were published in April 2013. In the Swiss-AMI trial,¹ intracoronary delivery of bonemarrow-derived mononuclear cells (BMC) in the presence of an AMI did not improve left ventricular ejection fraction (LVEF), irrespective of whether cells were infused 5–7 days or 3–4 weeks after the ischaemic event. Conversely, in the CELLWAVE trial,² the use of BMC in combination with pretreatment of the cardiac area with low-energy ultrasound shock waves led to a modest, but significant, increase in LVEF, and a decrease in the number of major adverse cardiac events in patients with chronic HF. More-dramatic, positive changes in systolic function and composite clinical score than those in the CELLWAVE trial were observed in similar patients in the C-CURE trial.³ Participants in this study received intramyocardial injection of bonemarrow-derived mesenchymal stromal cells (MSC) that had been exposed to a 'cocktail' of cardiogenic growth factors to promote the nuclear expression of myocyte-specific enhancer factor 2C (MEF2C).³

The recognition, nearly 12 years ago, that c-kit-positive haematopoietic stem cells (HSC) have the inherent ability to repair the infarcted myocardium in experimental models⁴ has profoundly affected cardiovascular research and clinical cardiology. These observations raised the possibility that HSC retain a remarkable degree of developmental plasticity and can generate cardiomyocytes and coronary vessels, a process that seems to contrast with their assumed predetermined lineage specification. During prenatal life, stem cells undergo a hierarchical progressive restriction of developmental options, and this mechanism of embryonic determination was thought to be irreversible and inviolable in adulthood. The unanticipated plasticity of adult HSC to form cells beyond their own tissue boundary has become the driving force of a series of clinical studies, in which bone marrow cells have been introduced as an experimental therapy in the management of an acutely infarcted or chronically failing heart.⁵

Data from a 2012 meta-analysis strongly support the view that various classes of BMC reduce left ventricular dysfunction, infarct size, ventricular remodelling, and mortality in

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Competing interests

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patients with ischaemic heart disease.⁵ However, the inconsistency in clinical outcome observed in some studies attenuates the enthusiasm for this experimental therapeutic approach. A good example is given by two of the studies discussed here—the Swiss-AMI trial¹ showed no benefit of BMC therapy, whereas the CELLWAVE trial² provided unequivocal positive effects of this approach in chronic ischaemic cardiomyopathy. The addition of shock waves to BMC in the CELLWAVE study does not change the fact that this class of cells has previously been shown by the group from Frankfurt, Germany, to be beneficial in patients with AMI and chronic HF.⁵

Several variables can be identified in an attempt to reconcile the differences in the results of these studies. However, the simplest, and most-probable, explanation relates to the preparation and characteristics of the BMC used in the trials. BMC should not be confused with HSC; only an undetermined, minute number of cells in the BMC pool might possess properties of HSC. Experimentally, remarkable levels of myocardial regeneration after infarction have been obtained with HSC, but not with BMC.⁶ The concept that factors released from BMC activate resident cardiac stem cells (CSC), indirectly inducing cardiac repair, is an attractive possibility. This growth response, however, could expand the surviving myocardium where viable CSC are present.⁷ The potential paracrine effect mediated by BMC is unlikely to promote the migration of CSC from the spared myocardium to the necrotic or scarred tissue, initiating a process capable of restoring the structural and functional integrity of the infarcted heart. Similarly, the recruitment of circulating progenitor cells is modest, at best, pointing to the delivered cells as the critical determinant of a successful clinical trial.

This philosophy was followed in the C-CURE study.³ Before intramyocardial injection, MSC were guided *in vitro* to express, in part, markers of cardiomyocyte commitment.³ This strategy was developed in an effort to ensure that the injected cells were primed to generate muscle mass and improve ventricular performance in patients with chronic HF. A substantial number, but not all, MSC were positive for MEF2C. Therefore, the delivered cells retained the ability to secrete a variety of growth factors known to activate resident CSC,⁸ which might have contributed to cardiac repair and the recovery of systolic function observed 6 months after treatment.³ The CHART-1 trial, which is designed to ascertain whether this novel approach of lineage specification in cell therapy is beneficial in chronic HF, has been approved and patients are currently being recruited.

The human heart contains a pool of CSC that can be harvested from small samples of myocardium and, after their increase *in vitro*, delivered back to patients by intracoronary infusion.⁹ This approach has been implemented in a phase I clinical trial involving 20 patients with chronic HF of ischaemic origin.¹⁰ This study is nearing completion, with very encouraging results. In addition, functionally-competent CSC for subsequent autologous delivery can be obtained from myocardial biopsies of patients with advanced heart failure, who are undergoing either cardiac transplantation or implantation of a left ventricular assist device. Thus, autologous CSC therapy is feasible and can be considered for research evaluation in patients with advanced heart failure. The dilemma now emerging in clinical cardiology is whether tissue-specific adult stem cells are superior, equally effective, or inferior to BMC, HSC, MSC, and guided MSC (Figure 1).

This question is difficult to answer, and only direct comparisons of cell categories will provide information fundamental for the future of cell therapy in humans. Importantly, CSC, HSC, and guided-MSC cannot be implemented in the setting of acute cardiac events in view of the time required for their preparation. BMC are an appealing medium for cell intervention, because these cells can be easily collected from bone marrow aspirates or from the peripheral blood after mobilization from the bone marrow with cytokines. However, this

apparently simple protocol could be more complex than previously anticipated, as emphasized by the discrepancy in the results of some clinical studies.⁵

Our view is that cardiac cell therapy needs to become more sophisticated. A collective effort needs to be made to introduce stem cell classes that engraft, divide, and differentiate within the damaged myocardium to acquire the myocyte, and vascular smooth muscle and endothelial cell lineages. The muscle mass and the coronary microcirculation need to be reconstituted in synchrony to achieve the form of cardiac repair that translates into functional benefit. Cardiomyocytes or vessels alone cannot restore regional ventricular performance. Both components are needed to replace the injured tissue with newly generated myocardium that is integrated structurally and functionally with the unaffected region of the ventricular wall.

At present, only two classes of cells—CSC and HSC—are multipotent and meet the criteria for ‘cardiopoietic stem cells’ (a term introduced by the C-CURE investigators³). HSC might have growth potential superior to that of CSC, but transdifferentiation could affect this characteristic. On the other hand, CSC might constitute a more-powerful form of therapy for cardiac repair than HSC. The process of transdifferentiation could alter the growth behaviour of HSC, which might then partly lose their capacity to divide through alterations of the telomere–telomerase system, premature cellular senescence, and apoptosis.

Potentially the most powerful and logical choice of cell for tissue reconstitution is the primitive cell that resides in the adult human heart.⁹ The appreciation that the heart is a dynamic organ, in which cell populations are constantly renewed by CSC activation and differentiation, has changed the old view of cardiac pathophysiology. Understanding the mechanisms of cardiac homeostasis offers the extraordinary opportunity to harness this naturally occurring process, and promote myocardial regeneration after injury.

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Figure 1.

Several cell types have been implemented clinically to promote myocardial regeneration. The possible mechanisms of action are indicated. Abbreviations: BMC, bonemarrow-derived mononuclear cell; CSC, cardiac stem cell; EC, endothelial cell; GF, growth factor; HPC, haematopoietic progenitor cell; HSC, haematopoietic stem cell; MSC, mesenchymal stromal cell; SMC, smooth muscle cell.