Bone marrow cell therapy after myocardial infarction. What should we select?

Landmesser, U
Bone marrow cell therapy after myocardial infarction –

What should we select?

Ulf Landmesser, MD

Cardiovascular Center, University Hospital Zurich and
Cardiovascular Research, Institute of Physiology, University of Zurich,
Zurich, Switzerland

Total word count: 1,482

Address for correspondence:
Ulf Landmesser, MD
University Hospital Zurich
Cardiovascular Center
Raemistrasse 100
8091 Zurich
SWITZERLAND
Phone: 0041-44-255-9595
Fax: 0041-44-255-4251

Subject codes: Bone marrow; Stem cells; cell therapy; myocardial infarction; CD34+
The promise of a stem/progenitor cell-mediated cardiac repair after myocardial infarction has fascinated basic scientists and clinical cardiologists alike, and initial small- and intermediate scale clinical studies have examined the effects of a single intracoronary administration of unfractionated or mononuclear bone marrow cells (BMCs) on left ventricular (LV) function in patients after myocardial infarction. Several recent meta-analyses of these controlled clinical studies have suggested a moderate, but significant improvement of LV ejection fraction by BMC therapy in patients after myocardial infarction (MI).1, 2 The most recent meta-analysis by Martin-Rendon et al. reported an improvement in LV ejection fraction of 2.99 % in patients undergoing BMC therapy after MI.2 This was close to the observed improvement in LV ejection fraction of 2.5 % in the REPAIR-AMI (Remodeling in Acute Myocardial Infarction) trial, the largest randomised, controlled clinical study of BMC therapy in patients after MI.3 Although these potential effects of BMC therapy on LV function are less than many investigators were hoping for, it should be noted that several of our established clinical therapies with an impact on prognosis in patients with myocardial infarction and a reduced LV function, such as ACE inhibitor or beta-blocker therapy, are associated with similar improvements in LV ejection fraction4 and have been observed in patients after MI with a less optimal background therapy as compared to present studies. There are, however, many remaining open questions with respect to mechanisms of stem/progenitor cell therapy after MI and potential strategies to optimise its effects.

As far as now, bone marrow-derived cells have either been used unfractionated or as mononuclear cells in clinical studies in patients after MI. This clearly represents a heterogeneous population of cells, so that it remains unclear which of the containing cells is particularly important for potential effects on cardiac repair. In the present issue of the European Heart Journal Tendera et al. report the results of the REGENT trial (Myocardial Regeneration by Intracoronary Infusion of Selected Population of Stem Cells in Acute Myocardial Infarction), a multicenter study comparing the effect of unselected bone marrow mononuclear cells with an approximately 100-times lower number of selected CD34+/KDR+ bone marrow-derived mononuclear cells in patients after myocardial infarction (Figure 1).5 The rational for selecting CD34+/KDR+ cells was based on the observation from clinical studies that these cells are mobilised from the bone marrow in response to myocardial ischemia6 and from experimental studies indicating that these cells may express endothelial and cardiac lineage markers.7

Although 200 patients were randomized to intracoronary infusion of unselected (n=80) or selected (n=80) mononuclear BMCs or to the control group (n=40) without BMC therapy, the primary endpoint of the study was evaluated in 117 patients, i.e. in 58.5 % of the patients included the study. The primary endpoint was defined as change of LV ejection fraction and volumes as measured by MRI before and 6 months after the procedure. In the single analysis of each cell-therapy group LV ejection fraction increased significantly by approximately 3 %, that was not observed in the control group, however, the absolute differences between the groups did not reach statistical significance after Bonferroni correction. A possible explanation for the lack of significance between the groups may be a reduced power of the study, due to the analysis of the primary endpoint in less than 60 % of the patients and a smaller change in LV ejection fraction after BMC therapy than expected when the study was planned (expected change of LV-EF >5%). This may be supported by the observation, that the magnitude of the change of LV ejection fraction in the cell therapy groups corresponds well to what has been reported in the above meta-analyses and the largest randomised study in the field, the REPAIR-AMI trial.3 We have therefore to interpret the results of the
REGENT trial with caution, since a limited power of the study may have prevented to show a significant difference for the primary endpoint, as has been pointed out by the authors.

Interestingly, the analysis of potential factors favouring the effect of BMC therapy on LV function in the REGENT trial revealed that a significant increase of LV ejection fraction was only observed in patients treated with BMCs who had a baseline LV ejection fraction below the median (i.e. LV-EF<37%). This corresponds well to the observation in the REPAIR-AMI study, that patients with a lower baseline LV ejection fraction derived most benefit. Therefore, these analyses are hypothesis-generating that selecting patients with a severe impairment of LV ejection fraction after myocardial infarction may be one way to increase the benefit of this therapy.

The study design of Tendera et al. did not compare similar numbers of unselected and selected BMCs (the number of selected BMCs was approximately 100-times lower), and the “selected” cells remained contained in the unselected BMCs. Such a selection of subfractions of BMCs would be expected to augment the effect of cell therapy on cardiac function only when there are other cell fractions within BMCs that would exert an inhibitory effect on cardiac repair, that remains largely unknown at present. However, a similar increase of LV-EF with unselected cells and selected cells of a substantially lower number would argue for an important role of the selected cell population for the effects on cardiac function.

The mechanisms whereby bone marrow-derived cell therapy may improve cardiac function are still debated and not entirely clear. Whereas initial experimental studies had suggested a rapid transdifferentiation of bone-marrow-derived stem cells (c-kit+, lineage-) into cardiomyocytes after cardiac injection post-myocardial infarction, likely inspired by the concept of a high stem cell plasticity of adult stem cells, later experimental studies using genetic techniques to follow bone marrow cell fate reported that transdifferentiation of bone-marrow-derived stem cells into cardiomyocytes did not explain the observed effects of bone marrow-derived stem cells on LV function, and suggested that BMCs rather act by paracrine mechanisms to improve cardiac function, such as by stimulation of capillary growth, prevention of cardiomyocyte apoptosis or stimulation of resident cardiac stem cells. In fact, inhibition of endogenous mobilisation of bone-marrow-derived stem cells after experimental myocardial infarction augmented myocardial damage after MI and resulted in an impaired capillary growth in the infarct border zone. The debate of the concept of stem cell plasticity, i.e. whether adult stem cells in addition to pluripotent stem cells can transdifferentiate into non-organ specific cell types, is not unique to the cardiovascular field. Similarly, several groups had observed that adult bone marrow-derived stem cells repaired damaged liver tissue, that was initially suggested to result from transdifferentiation into liver cells, but later was reported to be a consequence of cell fusion with liver cells. Cell fusion has also been suggested to explain in part the discrepant findings with respect to the transdifferentiation potential of BMC into cardiomyocytes. Whether strategies to enhance cardiomyogenic differentiation of adult stem/progenitor cells, i.e. by activation of cardiogenic Wnt pathways or by small molecules or whether induction of pluripotency will be required to efficiently enhance cardiomyogenesis remains one of the important future challenges.

While the initially perceived rapid chance for a complete cardiac repair by stem/progenitor cell therapy after MI has generated high expectations, now the potential of this therapy needs to be carefully developed by addressing important remaining questions, including the optimal cell types and preconditioning, the timing and dosing of cells to be used, how to augment the functional repair capacity of transplanted cells and how to optimise their homing and
engraftment in the heart and how to select the patients that may benefit most from this therapy. An important focus of present basic and clinical studies is therefore directed towards optimising the outcome and effect of stem/progenitor cell-based therapies, such as by improving stem/progenitor cell repair capacity and the process of cardiac cell homing. Notably, vascular and pro-angiogenic repair capacity of autologous stem/progenitor cells is reduced by cardiovascular risk factors, such as diabetes and by aging, likely representing an important potential target for optimisation of cell-based therapy. A reduced nitric oxide (NO) production by both, circulating and bone-marrow-derived stem/progenitor cells has been suggested to be critical for their reduced in vivo repair capacity. Augmented expression of endothelial NO-synthase by gene transfer into endothelial progenitor cells prior to cardiac transplantation is currently explored in the clinical ENACT-AMI trial as a strategy to augment cell repair capacity. Furthermore, several strategies are examined to improve homing and engraftment of mobilised stem/progenitor cells, i.e. the SITAGRAMI trial. Moreover, the timing and dosing of cell transplantation may be relevant for the effect of BMC therapy after MI, that is currently examined in the SWISS-AMI and BOOST-2 trials.

Whereas the present clinical studies of BMC therapy have largely examined the effect on LV ejection fraction, i.e. a surrogate endpoint, ultimately, the validation of cardiac cell therapy for clinical use will depend on the demonstration of a benefit with regard to clinical outcomes, similar as with reperfusion therapy. In this respect, besides optimising the conditions of cell therapy, selection of the patients who may benefit most from this therapy, i.e. based on LV ejection fraction and other parameters, will likely be an important issue to adequately examine the clinical potential of this novel therapeutic concept.

**Figure legend**

The REGENT trial examined the effect of a single intracoronary administration of either unselected or CD34+/CXCR4+ selected bone-marrow-derived mononuclear cells on the change of LV ejection fraction and volumes after myocardial infarction (as compared to a control group without BMC therapy). The number of selected BM cells was approximately 100-times lower as compared to unselected BM cells. This is the first clinical study aiming to examine which cells contained in bone marrow are particularly important for potential effects on cardiac repair after MI.
References


