The problem is obvious, the solution is not: numbers do matter in cardiac cell therapy!

EXPERT’S PERSPECTIVE

Jochen Müller-Ehmsen*

Department of Internal Medicine III, Heart Center, University of Cologne, Kerpener Str. 62, Köln/Cologne 50937, Germany

Online publish-ahead-of-print 31 August 2012

This editorial refers to an article by Z. Pasha et al. published in Cardiovascular Research in 2008. It is accompanied by a retrospective editorial by two of the authors of that original article, Z. Pasha and M. Ashraf, pp. 210–213, this issue, as part of this Spotlight on Landmark Papers in Cardiovascular Research.

Cardiac cell therapy was first proposed in 1992 to be a valuable treatment option for myocardial infarction and heart failure. Meanwhile, many cell types and many routes of application have been studied, and many clinical studies have also been performed. The original approach of cardiac cell therapy was aimed at replacing lost cells by newly seeded cardiomyocytes or precursors thereof, which ideally actively contribute to cardiac contractility. This approach is hampered by the lack of sufficient cardiomyocyte resources and by the inability of bone marrow cells to transdifferentiate into heart muscle cells, by environmental influence only. A second approach of cardiac cell therapy appears easier to conduct, in which progenitor cells (e.g., bone marrow cells) are used as carriers of cytokines or other anti-oxidant formation agents that beneficially influence cardiac structure and function after myocardial infarction. This latter approach has already been studied extensively in clinical trials.

As for pharmacological treatment, for cell therapy the dose might also play a crucial role for its therapeutic success. And as in pharmacology, this is not simply a matter of the dose being applied, but also of the active dose at the site of action. In cell therapy, this translates into the number of persisting cells in the heart. While ‘It is the dose that makes a thing poisonous’ as Paracelsus (Philippus Aureolus Theophrastus Bombast of Hohenheim, 1493–1541) stated, a threshold dose must also be exceeded before any benefit of a drug can be expected. Thus far, it is completely unknown what this threshold dose might be in cell therapy, and certainly this dose is likely to be cell-type dependent.

The importance of cell persistence after cell therapy was recognized rather early during the exploration of cardiac cell therapy. In early studies with rat neonatal cardiomyocytes that were injected as a mixture of cardiomyocytes and non-cardiomyocytes, the number of persisting and surviving cells was rather high (>10%). However, with cardiomyocytes derived from embryonic stem cells or induced pluripotent stem cells or with mononuclear or mesenchymal bone marrow cells, these numbers could not be reached and cell persistence was as low as 1% after the first few days. Intracorony injection of cells, as often applied in clinical studies, results in even lower numbers than intramyocardial cell injection, no matter if a balloon is used to improve cell homing or not.

In their 2008 study published in Cardiovascular Research, Pasha et al. focused on the question of how cell persistence and survival after cardiac cell transplantation could be enhanced. They used bone marrow-derived mesenchymal stem cells (MSCs) that were preconditioned with stromal-derived factor 1 alpha (SDF-1), which is a CXCR4 agonist. This treatment prevented MSCs from cell death after oxidant-induced injury and enhanced viability when compared with control. Apoptosis of preconditioned MSCs was reduced, proliferation was enhanced, and VEGF release was higher. Most importantly, these in vitro data were confirmed by extensive in vivo analyses in which injection of preconditioned MSCs led to higher SDF-1 expression in ischaemic myocardium (mRNA), enhanced homing of MSCs at the site of infarction and in peri-infarct areas, higher numbers of c-kit-positive cells from bone marrow, higher density of capillaries, activation of PI3K and Akt pathways, reduction of apoptosis, reduction of scar size, and, finally, improvement in cardiac function by echocardiography. The effects of SDF-1 preconditioning were attenuated by the CXCR4 antagonist AMD, indicating the specificity of these observations.

This study was an important milestone, demonstrating that cytokine preconditioning has an impact on homing, survival, and the regenerative capacity of MSCs. The results perfectly complement other findings which demonstrated that the activation of Akt may be an important mechanism of cell protection in cardiac cell therapy. Meanwhile, there have been multiple reports and multiple attempts to further optimize cell therapy and especially cell persistence/survival by pharmacological interventions including several pro-survival cocktails. Furthermore, there is additional evidence that enhancing SDF-1 in the heart by pharmacological inhibition of SDF-1 cleavage (inhibition of CD26/dipeptidylpeptidase IV (DPP-IV)) improves homing of mobilized bone marrow cells and cardiac function after
myocardial infarction. Currently, this approach is being investigated in the SITAGRAMI trial.

In conclusion, cardiac cell therapy has reached a point at which we need to critically define our goals: cell replacement or cell protection? For either approach the number of cells that are successfully grafted does matter for treatment effects. Pasha et al. did recognize in their 2008 Cardiovascular Research publication that cytokine preconditioning of mesenchymal bone marrow cells enhances the paracrine potential and the protection from cell death and ultimately improves cardiac function after myocardial infarction. Many other studies support the importance of the SDF1/CXCR4 axis for improving survival and homing of grafted cells. Nevertheless, despite all this progress, we have not yet reached our goals. The clinical translation of these and other pre-clinical results, especially those derived from small-animal studies, remains most difficult. This is even more the case if our goal is defined as cell replacement, in which case the electrical integration of grafted cells becomes of similar importance as cell survival. Thus, Pasha et al. conducted one very important study, but many others need to follow, and combined efforts need to be taken, before cardiac cell therapy will become a successful therapy for heart disease in the future.

References