Early Cardiac Retention of Administered Stem Cells Determines Clinical Efficacy of Cell Therapy in Patients With Dilated Cardiomyopathy

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The diagnosis of nonischemic dilated cardiomyopathy (DCM) comprises a primary myocardial disease of various causes, which is characterized by left ventricular (LV) dilatation and impaired myocardial contractility. Although a broad range of pharmacological and device therapies are available, morbidity and mortality remain high in patients with advanced DCM. Thus, there is an urgent need for novel therapies aiming at functional regeneration of myocardial contractility in DCM. Although regenerative therapies using administration of a variety of different cell types have emerged as a promising approach to improve heart function in patients with ischemic heart disease, only a few pilot studies have investigated intracoronary application of autologous bone marrow–derived cells (BMC) in patients with DCM. Seth et al performed intracoronary infusion of BMC in 24 patients with DCM and reported a modest 5% increase in LV ejection fraction in parallel with an increased ratio of capillaries to myocytes as evidenced by endomyocardial biopsies at 6 months. In the TOPCARE-DCM pilot study including 33 patients, the improvement in global and regional LV contractile function was rather heterogeneous but was also paralleled by improved microvascular function as assessed by measuring coronary flow reserve at 3 months after intracoronary infusion of BMC.

In this issue of Circulation Research, Vrtovec et al now considerably extend these previous observations. The authors randomized 110 patients with DCM to either intracoronary delivery of CD34+ cells obtained by apheresis after granulocyte colony-stimulating factor–mediated mobilization or a control group. In the cell-treated group, LV ejection fraction and 6-minute walk distance significantly increased, whereas N-terminal probrain natriuretic peptide serum levels were reduced. The observed improvements occurred within the first year after cell application. The improvement in LV ejection fraction of 5.7 absolute percentage points translated into a better clinical outcome at 5 years, driven by a profound and significant reduction of pump failure–related death, despite the small patient numbers. Most importantly, in a subset of 43 patients receiving intracoronary cell infusion, early retention of the administered cells in the heart was investigated by labeling a fraction of the cells with 99mTc-hexamethylpropylenamine oxine and performing single photon emission computed tomography imaging 2 and 18 hours after the intracoronary delivery. Overall, on average 7% of the radioactivity was detected within the heart at 2 hours, which dropped to 5% at 18 hours after injection. Correlating the amount of cardiac cell retention with functional outcome at 3 and 12 months revealed that patients with above-average early cell homing demonstrated a significant increase in LV ejection fraction, whereas patients with poor cell retention did not show any improvement in LV function.

The results of the study by Vrtovec et al are unique and especially noteworthy for 2 reasons: first, the specific selection of the LV area targeted by the infused cells, and second, the correlation of early cell retention with subsequent functional outcome.

After 99mTc-sestamibi imaging, the coronary artery used for cell administration was selected as targeting viable LV segments with reduced tracer accumulation and contractile dysfunction indicative of coronary microvascular dysfunction. Indeed, severely reduced coronary flow reserve and impaired coronary microvascular function have been previously demonstrated in patients with nonischemic DCM. Furthermore, the degree of microvascular dysfunction is an independent predictor of clinical outcome, including death in patients with DCM. Experimental studies documented a crucial role for coordinated angiogenesis to prevent the progression from adaptive cardiac hypertrophy to heart failure in the absence of epicardial flow-limiting stenosis. Given that administration of BMC is experimentally well-established to contribute to increased neovascularization and stimulated angiogenesis in ischemic tissue, but does not directly contribute to the formation of new cardiac myocytes, it is conceivable that the profound effects of intracoronary CD34+ cells on both contractile function and long-term clinical outcome observed in the study by Vrtovec et al are secondary to improved microvascular function. Indeed, previous clinical studies have shown that administration of BMC or blood-derived cells is associated with improved microvascular function and a reduction in myocardial perfusion defects. Furthermore, the 2 previously published pilot trials of BMC administration in patients with DCM already suggested that LV contractile recovery is paralleled by improved coronary microvascular function. Thus, taken together, the presence of coronary microvascular dysfunction within the very heterogeneous potpourri of causes leading to DCM seems to contribute to identifying patients, who derive the most benefit from intracoronary infusion of blood- or bone marrow–derived cells.
The observation by Vrtovec et al.⁴ that early cell retention determines subsequent cardiac functional contractile recovery extends previous experimental work by Joe Wu’s group⁵ and, for the first time, clinically documents a dose–effect relationship for intracoronary cell therapy. Retention and homing of cells are mediated in large part by the interaction between the chemokine stromal cell–derived factor-1, which is known to be upregulated in the infarcted heart and in response to hypoxia,⁶,¹⁰,¹² and its receptor, CXCR4, which is expressed on blood- and bone marrow–derived cells and determines their functional activity for therapeutic neovascularization.¹⁷,¹⁸ Experimentally, the migratory capacity of administered BMC toward stromal cell–derived factor-1 correlates closely with their neovascularization capacity.¹⁹ Unfortunately, data on CXCR4 expression and functionality of the applied CD34+ cells are not given in the article by Vrtovec et al.⁴ Thus, it cannot be discriminated whether improved cell retention is because of better homing capacity of the infused cells or better retaining capacity of the target tissue. In patients with acute myocardial infarction, where stromal cell–derived factor-1 is maximally upregulated in the ischemic myocardium, the stromal cell–derived factor-1–induced migratory capacity of the applied cells correlates with infarct size reduction as measured by magnetic resonance imaging at 4 months,²⁰ as well as with long-term clinical outcome at 5 years.²¹ However, patients with DCM do not experience overt myocardial ischemia and injury, and thus, the retention signals emanated by the cardiac target tissue will most likely differ with the various causes of DCM, which is reflected by the considerable heterogeneity in response to cell therapy in individual patients with DCM. The discrimination between homing capacity of the cells and retention capacity of the cardiac target tissue is even more relevant because recent studies demonstrated that both cell homing capacity by ex vivo treatment of isolated cells and target tissue retention capacity by echo-guided in vivo pre-treatment can be modified to augment cell homing. Thus, the study by Vrtovec et al.⁴ not only demonstrates that intracoronary infusion of granulocyte colony-stimulating factor–mobilized CD34+ cells is indeed responsible for improved LV function and better clinical outcome in patients with dilated cardiomyopathy but also paves the way for the design of future clinical cell therapy trials optimizing treatment strategies by cell enhancement or cardiac target tissue preconditioning before cell administration.

References


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