Cardiac Cell Therapy
Lost in Meta-Analyses

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Heart failure is frequently called the new epidemic of the 21st century, since the prevalence of this malignant disease has remained high through the last decade, mostly driven by the increased survival of patients with large acute myocardial infarctions. Established therapies aim at reducing preload, afterload, and neurohumoral activation, as well as mineralocorticoid dysregulation. However, the underlying ongoing loss of cardiomyocytes, which is followed by fibrosis, is only marginally influenced.

Applying a scientific approach of using cell therapy generates new understandings for disease pathology, progression, and endogenous repair capacity. As part of a landmark investigation, the annual cardiomyocyte turnover-rate was estimated to be 1% in young adults, which decreases to 0.5% in the elderly, suggesting that approximately half of the heart’s muscle cells are renewed during lifespan. However, this endogenous repair capacity is not sufficient to cope with the loss of cardiomyocytes after acute myocardial infarction or other heart diseases. Enhancement of endogenous repair processes, optimally within a preconditioned microenvironment, would therefore offer unprecedented tools to enhance regenerative capacity and to modify adverse left ventricular remodeling.

Indeed, supported by preclinical studies, numerous phase I and phase II clinical trials have been initiated and completed for more than 10 years now, testing various cell types and application protocols in a huge heterogeneity of patient conditions. However, clinical progress in developing convincing and successful therapies was rather modest, which can in part be attributed to rather small, underpowered trials using surrogate endpoints and open-label treatment approaches carrying the risk of bias.

In an effort to overcome some of the mentioned limitations in power, Fisher and colleagues have published an updated systematic review of cell-based therapy in chronic heart failure in this issue of Circulation Research. Their meta-analysis is of excellent quality and adequately addresses the heterogeneity of included trials, the problem of missing data, and bias towards publication, reporting, and randomization. Importantly, they included only randomized controlled trials (RCTs) conducted in the presence of chronic heart failure, which allowed for inclusion of a total of 31 clinical trials covering 882 cell-treated patients and 639 control patients. The majority of trials (21) applied total bone marrow-derived mononuclear cells, including 8 trials using different subpopulations or G-CSF–mobilized mononuclear cells. However, the other trials applied bone marrow-derived mesenchymal stem cells (4), cardiac stem cells (1), skeletal myoblast-derived cells (4), or adipose tissue-derived regenerative cells (1). Of note, 3 trials with nonischemic, dilated heart failure were also included. In admirably detailed work, the authors analyzed not only clinical events but also surrogate markers for heart failure which were assessed in the included RCTs. In addition, a specific focus of the authors was assessment of the risk of bias. The primary endpoint of the meta-analysis, which was a composite of death and rehospitalization for heart failure, demonstrated a significant improvement during long-term follow-up (>12 months), with a mortality risk reduction of 52%, and risk reduction for rehospitalization of 61% in the cell-treated patients compared to control. Importantly, mortality was reduced in cell-treated patients compared to controls in every single included trial, but obviously, none of the trials were statistically powered to assess this endpoint. Likewise, the calculated effects of cell treatment on heart failure symptoms, left ventricular ejection fraction (LVEF), and other secondary outcomes like natriuretic peptide serum levels, 6-minute walk-test and quality of life, point to a marked improvement in patients treated with cell therapy compared to controls, although the individual pooled analyses comprise only 329 patients for LVEF and 209 patients for quality of life. However, when only double-blind studies are selected, the meta-analysis by Fisher and colleagues reveals that statistical significant differences between the cell-treated group and the control group are entirely lost.

A second meta-analysis, also published in this issue of Circulation Research, claims to derive entirely different conclusions, namely that cell therapy does not affect cardiac contractile function or left ventricular remodeling and does not influence clinical outcome in patients with acute myocardial infarction. In this study, 12 randomized controlled trials were included, all treating patients with different cell populations at different time points after acute myocardial infarction. What do we learn from these two meta-analyses with obviously opposing results?

Published Meta-Analyses Outnumber Well-Controlled Randomized Trials in Cardiac Cell Therapy
While meta-analyses may be well suited to overcome limitations in power of smaller sized phase II trials, extreme caution...
should be applied to the interpretation of their results specifically in the field of biological therapies, like cell therapies. As the presumed biological activity of a cellular product may greatly differ depending on cell source, cell preparation, and cell administration techniques, putting together all different trials into one basket is more than questionable. Moreover, as the microenvironment of the cardiac target tissue will certainly dictate mechanisms contributing to functional cardiac regeneration, specific attention should be paid to the patient population recruited into the different trials included into any meta-analyses. Based on this background, it is indeed worrisome that—according to a very recent PubMed search—the number of published meta-analyses of cardiac cell therapy by far outnumbers the number of well controlled randomized trials. While Fisher and colleagues meticulously address some of the caveats mentioned above, the study of Gyongyosi et al pooled a variety of different cell types clinically used into one single analysis. Of the 12 trials included into the analysis of Gyongyosi et al, one used CD-133 enriched bone marrow cells, one CD34/CXCR4 enriched bone marrow cells, one cardiosphere-derived cardiac cells, six trials used ficoll-gradient isolated bone marrow-derived cells, one sedimentation isolated bone marrow-derived cells, and two studies used an automated system to isolate bone marrow-derived cells. In addition, some of the trials stored the cellular product in nonbuffered saline supplemented with heparin, a condition which prevents homing and functional activity of bone marrow-derived cells in animal models. Moreover, timing of cell administration varied between 24 hours postacute myocardial infarction (AMI) to 3 months after AMI, thus including the convalescent period postmyocardial infarction, where the microenvironment of the target tissue is totally different. In analogy to meta-analyses of drug therapy trials, would anyone dare to perform a single meta-analysis with different drugs given at different time points and at different doses?

Of even greater concern, although Gyongyosi et al are to be complimented for performing an analysis based on individual patient data rather than relying on published data, the fact that only ≥60% of all patients included into intracoronary cell administration trials in acute myocardial infarction could be recruited for the study as well as the rather short-term follow-up of 6 months for clinical outcome data (in the majority of patients) severely limits the conclusions to be drawn by this study. Taken together, specifically in the field of cardiac cell therapies, meta-analyses can be hypothesis-generating at best, but by no means hypothesis testing.

A Plea for Prospective Well-Controlled Large Clinical Outcome Studies

Notwithstanding all these limitations and potential shortcomings, both meta-analyses convincingly documented the safety of cell therapy in patients with acute myocardial infarction or chronic heart failure. Based on the excellent safety of cell therapy, it appears to be prudent and timely to prospectively test the hypothesis that cell therapy is associated with reduced mortality and rehospitalization as well as improved heart failure-specific endpoints and symptoms in large, appropriately randomized, well-controlled clinical outcome trials. An example of such an effort is the currently recruiting BAMI trial (NCT01569178), a phase-III pan-European trial investigating the effects of autologous BMC (bone marrow-derived mononuclear cells), compared to standard treatment, in the setting of large acute myocardial infarction. In patients with chronic heart failure, there are currently three recruiting studies with clinical outcome endpoints, namely CHART-1 investigating intramyocardial injection of autologous cardiopoietic cells (NCT 01768702), the REPEAT trial comparing single with repeated intracoronary infusion of autologous bone marrow-derived cells (NCT01693042) and a trial using intramyocardial injection of allogenic mesenchymal precursor cells (NCT02032004). However, as long as data of large outcome trials with well-defined and functionally active cellular products are not available, cardiac cell therapy should be viewed as an experimental therapeutic approach, regardless of potential hypothesis-generating data derived from meta-analyses.

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Disclosures

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References


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