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Myocardial regeneration therapy in heart failure: Current status and future therapeutic implications in clinical practice

Marko Banovic [a,b], Maja Pusnik-Vrckovnik [c], Eleni Nakou [d], Panos Vardas [d,*]

[a] Cardiology Department, University Clinical Center of Serbia, Belgrade, Serbia
[b] Belgrade Medical School, Belgrade, Serbia
[c] General Hospital Slovenj Gradec, Slovenj Gradec, Slovenia
[d] Cardiology Department, University Hospital, Crete, Greece

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ABSTRACT

Despite multiple treatment regimens the morbidity and mortality of patients with advanced heart failure (HF) have reached pandemic proportions. In an effort to address the root cause of the problem, curative strategies are increasingly being considered. A case in point is the evolution of regenerative medicine technologies aiming to halt or even reverse progressive organ deterioration in the HF setting.

The prevailing unmet clinical needs in HF therapy have provided a major incentive for the development of cell-based treatment strategies, which have shown encouraging results in experimental studies. In turn, this has led to a significant international effort in cell-based clinical trials. In order to translate the promise of biotherapies into clinical benefit many more questions need to be addressed.

In this review we analyze current clinical experience regarding cell therapy in the setting of ischemic/nonischemic HF and address key issues that could be a guide for future successful cell-based therapeutic application in HF patients in clinical practice.

1. Introduction

Despite multiple treatment regimens the morbidity and mortality of patients with advanced HF have reached pandemic proportions. The evolution of regenerative medicine technologies aiming to halt or even reverse progressive organ deterioration in the HF setting appears a challenge in HF therapy.

The prevailing unmet clinical need has provided a major incentive for the development of cell-based treatment options, which have shown encouraging results in experimental studies. In turn, this has led to a significant international effort in cell-based clinical trials. Most clinical trials have focused on the implementation of cell therapy in acute/subacute ischemic heart disease, targeting prevention of HF induction [1]. However, experience is much more limited in the setting of chronic, florid heart failure of different origins [1–3]. Apparently, cell therapy in HF patients has yet to fulfill their considerable promise. In this review we analyze current clinical experience regarding cell therapy in the setting of ischemic/nonischemic HF and address key issues that could be a guide for successful application of cell-based therapies in HF patients in the future.

2. Cell therapy in ischemic heart failure: a current perspective

In the last decade numerous trials in the setting of ischemic HF, including autologous and allogeneic cell implantation and different cell types, have been published. Still, the results were inconsistent and clear evidence that cell therapy in patients with ischemic HF is an effective treatment which improves survival has not been given. Below we consider the main reasons that may be responsible for the lack of expected benefit from cellular treatment in the setting of ischemic HF.

2.1. The cell issue

Inflammation, proliferation of stromal and vascular cells and scar formation may determine the cardiomyocyte turnover after cardiac injury [4]. There is evidence suggesting that cell-based therapies with cells of various origins affect endogenous cardiomyocyte renewal or directly produce new cardiomyocytes from the transplanted cells conferring, consequently, therapeutic benefits to the injured heart [4].

The degree of cardiomyocyte renewal depends on the cell type, the retention and survival of those cells within the heart. In the ischemic HF setting bone marrow derived mononuclear cells (BMMNCs) are most widely used, given easy harvest and absence of need for ex vivo expansion. The BM contains several cell populations that have the capacity to proliferate, migrate, and also differentiate into various mature cell types. Among these cells are hematopoietic cells (HCs), mesenchymal stem

* Corresponding author at: Department of Cardiology, Heraklion University Hospital, 7100, Voutes, Heraklion, Greece.
E-mail address: cardio@med.uoc.gr (P. Vardas).

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cells (MSCs) and endothelial progenitor cells (EPCs), while the possibility to purify and select expanded cell populations allows a more specific use of cardiac cell therapy. It is worth noting that closer scrutiny of EPCs indicates that these are monocyte/macrophages that participate in blood vessel formation but not transdifferentiate into cell types of the vessels. A recent consensus on current EPC nomenclature supports the terminology endothelial colony forming cells (ECFCs) and myeloid angiogenic cells MACs [5], as MACs do not give rise to endothelial cells albeit with potent pro-angiogenic, vasoreparative functionality, while ECFCs represent an endothelial cell type with potent intrinsic angiogenic capacity capable of contributing to de novo, in vivo blood vessel formation [5].

Since only a small proportion of injected cells is retained in the myocardium, the logical presumption is that the total number of cells injected may influence the degree of cardiac recovery, but this is yet to be proven. A meta-analysis revealed that the mean changes in left ventricular ejection fraction (LVEF), infarct size, and left ventricular end-diastolic volume (LVEDV) were similar in patients who received $>100 \times 10^6$ BMCs (the median number in included studies) and $<100 \times 10^6$ BMCs, but there was a greater reduction in left ventricular end-systolic volume (LVESV) in patients who received $<100 \times 10^6$ BMCs [6]. Further analysis with progressively lower bone-marrow cell (BMC) numbers failed to demonstrate favorable outcomes (improvement in LVEF, and reduction in infarct size, LVESV, and LVEDV). Interestingly, recently published results of CHART-1 trial [7] demonstrated greater benefit with lower number of injections (<19 injections). Possible explanations for this finding included local myocardial damage from the multiple injections, compression from the volume injected, and the number of cells delivered.

Although the quest for the 'ideal' cell is still ongoing, experimental head-to-head comparisons [8–10] suggest that the best outcomes are achieved by cells that are phenotypically as close as possible to those targeted for rescue and, importantly, this observation is concordant to the above described paracrine mechanism. Consequently, the newer generation of clinical trials has entailed transplantation of cells committed to a cardiac lineage including right atrium-derived c-kit+ cells, cardiosphere-derived cells harvested from the right ventricle, and BM derived mesenchymal cells engineered to express cardiac transcription factors [11–13]. Interestingly, Li TS et al. compared human cardiosphere-derived cells (CDCs), BM-derived mesenchymal stem cells, adipose tissue-derived mesenchymal stem cells, and bone marrow mononuclear cells in vitro for various assays of potency and in vivo for functional myocardial repair in the same mouse model of myocardial infarction [14]. By head-to-head direct comparison a functional superiority of heart-derived cells as compared to three types of adult stem cells of extracardiac origin was observed, which was consistent with their well-balanced secretion of paracrine factors as well as their higher cardiomyogenic differentiation capacity and engraftment [14]. However, further in vivo studies will be required to elucidate the precise mechanisms of functional superiority of CDCs.

2.2. The difference in delivery method

One of the crucial methodologic questions refers to the optimal mechanism of cell delivery to the heart. The two methods that have been widely used were intracoronary and intramyocardial cell delivery. Intramyocardial cell delivery has been performed by both surgical and percutaneous method (transendocardial) via transfemoral or transradial approach [15]. Couple of studies have documented the superiority of the epicardial delivery of a cell loaded patch over intramyocardial injections with regard to cell retention, survival and ultimately, preservation of heart function [16]. Some approaches have combined cell implantation with concomitant revascularization; however, these results will always be difficult to interpret conclusively without consideration of revascularization effects. Therefore, only "stand-alone cell treatment" for patients with ischemic HF has been analyzed in this review.

Comparing intramyocardial vs intracoronary delivery, the randomized REGENERATE-IHD [17] study found no significant differences in terms of safety and feasibility between the two delivery routes, with no significant difference in procedural complications or major adverse cardiac events. Nevertheless, there was a trend toward improved HF symptoms in the patients treated with intramyocardial delivery. Kandala et al. [18] concluded in their meta-analysis, which included 10 randomized trials with 519 patients, that intramyocardial injections may be superior to intracoronary infusion in patients with chronic ischemic LV systolic dysfunction. Thus, it seems that intramyocardial delivery method leads to a better engraftment of the cells. On the other hand, there is more potential for iatrogenic injuries like myocardial perforations and induced arrhythmogenesis but this might also be a related to the operator experience. Surgical intramyocardial delivery is the most direct but also the most invasive strategy, making the procedure extremely hazardous for complications, especially in the context of patients with severely reduced LVEF and number of serious comorbidities that might increase the risk of surgical procedure [19]. The surgical approach also limits access to certain areas of the LV such as the septum [20]. Even with the most direct injection method cell retention rates are typically not exceeding 10% of the injected dose [21] and thus still represent the Achilles heel in clinical translation of cell therapy.

2.3. Cell therapy in ischemic heart failure: the changing concept of the mechanism of action and proof of success

During the last couple of years the concept of cell therapy has been somewhat changed. Indeed, a hypothesis that was initially highly cell centric has undergone a fundamental re-evaluation, moving away from the premise of a direct exogenous cell-mediated regeneration toward the prevailing view that therapeutic activity reflects primarily an indirect, paracrine effect of delivered cells interacting with the diseased myocardium to trigger an endogenous regenerative cascade. The mobilization of progenitor cells from the bone marrow by administration of growth factors such as granulocyte colony stimulating factor (G-CSF) has attracted considerable interest. However, limited trials have shown favorable outcomes in terms of left ventricular remodeling and dysfunction [22,23] while others [24,25] have not been able to reproduce the beneficial outcomes observed in experimental models [26,27]. Of note, 2-deoxy-2-[18F]fluoro-d-glucose positron emission tomography (FDG-PET) revealed improved cardiac regeneration and attenuated adverse remodeling following sitagliptin and G-CSF therapy after acute myocardial infarction [28]. These variable outcomes observed in the trials may be attributed to several factors such as timing of G-SCF therapy, the route of administration, the age and comorbidities, which should be addressed in future trials to unravel the potential benefits of G-SCF therapy.

Recent reports indicate that only rarely do individuals with ischemic HF demonstrate clinical regenerative potency, largely due to the ultimate lack of cellular capability of repair [29]. One approach to address this issue is to preselect populations of younger allogeneic cells demonstrating cardio-regenerative capacity [30]. This was already indicated in Poseidon randomized trial, in which there was a trend toward lesser incidence of serious adverse events in patients treated with allogeneic cells [31]. Indeed, the aging-induced transition of HCs from polyclonal into monoclonal cells has a strong effect on stem cell competency during ischemia or infarction, while EPCs from elderly subjects display impaired proliferation, migration and survival as compared to young subjects, attributed to the altered turnover rate, susceptibility to apoptosis as well as impaired antioxidant defense and genomic instability [32]. Moreover, evidence suggests that epigenetic modifications classified into three main categories (DNA methylation, histone modification and non-coding RNA) are strongly related to impaired reparative potential of EPCs, BM-derived stem cells and mature ECs [32]. Viewing from the angle of epigenetics, age-related