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Review

Cell therapy for heart disease after 15 years: Unmet expectations

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ABSTRACT

Over the past two decades cardiac cell therapy (CCT) has emerged as a promising new strategy to cure heart diseases at high unmet need. Thousands of patients have entered clinical trials for acute or chronic heart conditions testing different cell types, including autologous or allogeneic bone marrow (BM)-derived mononuclear or selected cells, BM- or adipose tissue-derived mesenchymal cells, or cardiac resident progenitors based on their potential ability to regenerate scarred or dysfunctional myocardium. Nowadays, the original enthusiasm surrounding the regenerative medicine field has been cushioned by a cumulative body of evidence indicating an inefficient or modest efficacy of CCT in improving cardiac function, along with the continued lack of indisputable proof for long-term prognostic benefit.

In this review, we have firstly comprehensively outlined the positive and negative results of cell therapy studies in patients with acute myocardial infarction, refractory angina and chronic heart failure. Next, we have discussed cell therapy- and patient-related variables (e.g. cell intrinsic and extrinsic characteristics as well as criteria of patient selection and proposed methodologies) that might have dampened the efficacy of past cell therapy trials. Finally, we have addressed critical factors to be considered before embarking on further clinical trials.

Contents

Abbreviations: CVD, cardiovascular diseases; CCT, cardiac cell therapy; AMI, acute myocardial infarction; RA, refractory angina; CHF, chronic heart failure; BM-MNC, bone marrow mononuclear cells; SKM, skeletal myoblasts; EPC, endothelial progenitor cells; MSC, mesenchymal stem cells; CSC, cardiac stem/progenitor cells; ESC, embryonic stem cells; iPSC, induced pluripotent stem cells; PB, peripheral blood; LV, left ventricular; RCT, randomized controlled trials; EF, ejection fraction; IC, intracoronary; G-CSF, granulocyte colony-stimulating factor; CMR, cardiac magnetic resonance; CDC, cardiosphere-derived stem cells; VEGF, vascular endothelial growth factor; IM, intramyocardial; MACE, major adverse cardiac events; CABG, coronary artery bypass surgery; TSA, trial sequential analysis; MPC, mesenchymal precursor cells; HLA, Human Leukocyte Antigen; IV, intravenous; SDF-1, stromal cell-derived factor 1.

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1. Introduction

Cardiovascular diseases (CVD) are the leading cause of death wordwide [1]. In Europe, CVD account for 45% of all deaths (49% for women and 40% for men) and lead to more than 4 million people deaths every year (1.4 million before the age of 75 years) [2]. Unfortunately, mortality rates are continuing to increase over the decades [1], fuelling the engine of scientific interest directed towards the development of novel therapies.

Over the past 15 years, cardiac cell therapy (CCT) has emerged as a promising therapeutic strategy for the treatment of CVD considered to be of higher unmet need, including acute myocardial infarction (AMI), refractory angina (RA) and chronic heart failure (CHF).

Several cell types have been tested in preclinical animal models and in humans while others are about to be introduced into the clinical scenario. In particular, bone marrow mononuclear cells (BM-MNC) [3–5], skeletal myoblasts (SKM) [6], endothelial progenitor cells (EPC) [7], mesenchymal stem/stromal cells (MSC) [8], cardiac stem/progenitor cells (CSC) [9,10], embryonic stem cells (ESC) [11,12], and induced pluripotent stem cells (iPSC) [13] have been inoculated into the injured heart over the past two decades. Generally, all these cell types were injected as a single cell population; however, more recently, some investigators oriented their research on the combinatorial (combo) approach, with the rationale to exploit cell complementarity and the favorable features of each cell type.

Originally, it was thought that stem/progenitor cells might promote cardiac repair by differentiation into functional cardiomyocytes and vascular structures. Yet, except for iPSC-derived cardiomyocytes obtained by specific "cardiogenic cocktails" [14], there is still no consensus on the ability of clinically available cell types to create cardiomyocytes *in vivo*. Thus, today the original concept of cardiomyocyte differentiation has shifted towards a paracrine paradigm, according to which the efficacy of CCT is related to the capacity of cell therapeutics to secrete a variety of growth factors/cytokines exerting a protective effect on injured myocardium [15]. This concept encouraged investigators to develop cell-free approaches [16–19].

Whatever the precise mechanism of action of these cells, from an extensive review of the literature it emerges that the overall efficacy of CCT is inconsistent and modest albeit the safety clinical profile appears satisfactory. These results have dampened the initial euphoria about cell-based reparative therapy spreading scepticism and reluctance into the scientific community. However, it is important to highlight that CCT cannot be deemed negative on the basis of the results obtained to date since many critical issues and limitations have emerged over time. In particular, different variables regarding both cell therapeutics and patients might have influenced clinical outcomes.

In this review, we have i) provided a comprehensive and critical assessment of the large body of work on the use of stem/progenitor cells in heart regeneration, ii) discussed the main factors that may have negatively impacted the success of these studies, and iii) addressed the future directions that scientists should undertake to increase the likelihood of CCT success.

2. A reappraisal of CCT trials

2.1. Acute myocardial infarction

In the last 15 years, more than 1500 AMI patients received therapeutic delivery of bone marrow (BM) or mobilized peripheral blood (PB) cells, with the aim to prevent or minimize post-infarction left ventricular (LV) remodeling by directly or indirectly promoting cardiac repair. Different regenerating cells were administered and, among them, BM-MNC were the most widely investigated.

Several randomized controlled trials (RCT) using BM-MNC have shown positive results in respect to global and regional LV ejection fraction (EF), infarct size and mortality [4,20–24]. For example, the BOOST [4], REPAIR-AMI [20] and BALANCE [22] trials proved that intracoronary (IC) injection of BM cells in patients with AMI promotes LVEF improvement, especially in patients with severely depressed cardiac function at baseline [20,25]. Of note, the benefit of cell therapy was sustained up to 5-years in the BALANCE trial but not in the BOOST trial [26]. Positive results were also demonstrated in other two studies in which cells were directly injected into the myocardium [27,28]. These encouraging findings were not confirmed in other studies [5,25,29–33] that found no differences in cardiac parameters in patients treated with BM-MNC. Similarly, negative results were observed in clinical trials which aimed to establish the optimal timinig of cell delivery in AMI patients. Specifically, the TIME [31], the lateTIME [32] and more recently, the REGENERATE-AMI [34] trials failed to prove the superiority of early (3-7 days) and/or late (2–3 weeks) cell delivery approach in the treatment of AMI. More definitive answers will likely come from the on-going BAMI trial (NCT01569178), the largest RCT (3000 patients to be enrolled) evaluating the effect of BM-MNC on all-cause death in AMI patients.

In the attempt to find other strategies to empower the efficacy of cell therapy, other investigators employed the BM-mobilizer granulocyte colony-stimulating factor (G-CSF). Data collected in the MAGIC [35], MAGIC Cell-3-DES [36] and TECAM [37] trials demonstrated that the administration of i) BM-MNC alone, ii) G-CSF alone or iii) G-CSF *plus* BM-MNC does not improve global or regional LV functions. Conversely, in the STEM-AMI trial we found that G-CSF alone attenuates LV remodeling at 3 years following large ante-

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