MAYO CLINIC

Breakthroughs in Cell Therapy for Heart Disease: Focus on Cardiosphere-Derived Cells

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CME Activity

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Abstract

The clinical reality of cell therapy for heart disease dates back to the 1990s, when autologous skeletal myoblasts were first transplanted into failing hearts during open-chest surgery. Since then, the focus has shifted to bone marrow–derived cells and, more recently, cells extracted from the heart itself. Although progress has been nonlinear and often disheartening, the field has nevertheless made remarkable progress. Six major breakthroughs are notable: (1) the establishment of safety with intracoronary delivery; (2) the finding that therapeutic regeneration is possible; (3) the increase in allogeneic cell therapy; (4) the effect of increasing mechanistic insights; (5) glimmers of clinical efficacy; and (6) the progression to phase 2 and 3 studies. This article individually reviews these landmark developments in detail and concludes that the field has reached a new phase of maturity where the prospect of clinical impact is increasingly imminent.

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Each year, approximately 1 million Americans have a myocardial infarction (MI).[1] Although acute mortality has decreased in recent decades because of the universal adoption of reperfusion therapy,[2] up to 36% of MI survivors will develop heart failure (HF) and consequently be at increased risk for premature death.[3] Whether due to MI or another cause, HF affects approximately 5 million Americans.[1] Patients are unable to exercise normally (in the extreme, they become bedbound) and experience shortness of breath. Current therapy relies on drugs that block various maladaptive signaling pathways, such as β-adrenergic blockers and angiotensin inhibitors. Additional benefit can sometimes be gained from pacemakers that attempt to normalize the pattern of cardiac contraction. Although such drugs and devices can attenuate the progression of HF, no treatment modality currently

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available addresses the root cause, which is a loss of functional heart muscle.[4] Cell therapy for heart disease aims to regenerate viable myocardial tissue that has been lost to disease. The main targets to date have been MI and HF. In the case of MI, the goal is to avert the progression to HF; in already established HF, cell therapy seeks to halt further deterioration or even to reverse the disease. Clinical trials have resulted in inconsistent partial restoration of cardiac structure and function,[5] giving cause for optimism but leaving much room for improvement.

In reflecting on the field, I have identified 6 major developments that have the potential to shape future progress. Time will tell just how durable these developments are and whether they will ultimately be hailed as genuine breakthroughs, but this article lists and discusses them one at a time. The perspective is personal, as will be evident from the fact that the work highlighted in 3 of the 6 bullets is my own. Nevertheless, I attempt to temper what may be seen as self-congratulatory enthusiasm with a number of caveats and concerns regarding the vast remaining gaps in our knowledge.

BREAKTHROUGH 1: ESTABLISHMENT OF SAFETY WITH INTRACORONARY DELIVERY

Skeletal myoblasts were the first cells to be applied to heart disease, on the logical premise that autologous satellite cells might develop into mature contractile units when implanted ectopically into the diseased heart.[6] The paradigm involved harvesting skeletal muscle biopsy specimens from patients with HF who were to undergo elective cardiac surgery; myoblasts would be grown ex vivo and then reimplanted by direct intramyocardial injection at the time of surgery. Despite early enthusiasm regarding this therapy, skeletal myoblasts eventually proved to be risky (ventricular arrhythmias were frequent) and without much functional benefit: the 300-patient phase 2 Myoblast Autologous Grafting in Ischemic Cardiomyopathy (MAGIC) trial was halted after an interim analysis of the first 97 randomized patients revealed no robust trend to efficacy.[7]

Since then, the focus has shifted to other cell types and to percutaneous catheter–based delivery methods. In 2001,[8] the first acute MI patient was treated with bone marrow–derived mononuclear cells (BMMCs). The paradigm has been oft-repeated and, collectively, forms the basis for the most substantive clinical experience to date with cell therapy for heart disease. After conventional intervention to restore patency of the occluded coronary artery, patients undergo bone marrow aspiration for derivation of BMMCs. The cells are rather finicky: details of manufacturing importantly influence potency, likely contributing to heterogeneous results among trials.[9,10] Typically, 1 to 14 days after MI, BMMCs are reintroduced into the patient via the intracoronary route using a balloon catheter inflated at the site of the initial blockage.

The salient finding has been the superior safety record of intracoronary BMMCs. Figure 1 shows the results of a meta-analysis of 7 trials that involved 660 patients.[11] Compared with baseline, BMMC transfer performed 4 to 7 days after MI decreased revascularization, cumulative clinical events of death or recurrent MI, culprit artery restenosis, and ventricular arrhythmia. The lack of excess arrhythmias in BMMC-treated patients is particularly notable. Although BMMCs are the only cell type for which results for large numbers of patients are available, the general pattern of safety with intracoronary delivery has held up so far with cardiac-derived cells as well.[12-14] One feature that BMMCs and cardiac-derived cells share is a predominantly indirect mechanism of action: long-term engraftment is not required for durable benefit.[15-17] The problem of arrhythmia is related to conduction block and inhomogeneity of repolarization; these factors are likely to be much more severe with skeletal myoblasts (that do not integrate electrically in the myocardium) or pluripotent cell–derived products. Indeed, Cingolani and I[18] have speculated that indirectly acting cells will be less arrhythmogenic than those that engraft, differentiate, and proliferate in vivo. The idea is that endogenous regeneration is likely to cause less electrical instability than transplantation of highly proliferative cells; the latter may colonize the heart, producing barriers to conduction and/or aberrant repolarization. The finding that intracoronary delivery of nonengrafting cells is safe, particularly with regard to arrhythmia, represents a major breakthrough for the field of cell therapy.