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ecent clinical trials have demonstrated the safety and potential benefits of the stem cell based therapies for the preservation and treatment of cardiac dysfunction following acute myocardial infarction.1,2 More recently Assmus and colleagues published the TOPCARE-CHD trial in which they compared the effects of infusing circulating progenitor cells to bone marrow mononuclear cells in patients at a time remote from acute myocardial infarction (average time from AMI to infusion, 6 to 7 years).3 Using a crossover clinical trial design that study demonstrated that circulating progenitor cells offered no benefit, where as infusion of whole bone marrow mononuclear cells resulted in an increase of 2.9% in the ejection fraction compared with a loss of 1.2% in control patients.3 The observation that circulating progenitor cells and bone marrow mononuclear cells lead to improved function in acute myocardial infarction,4 but only bone marrow derived progenitor cells led to improvement at times significantly remote from AMI suggest that different cell populations or delivery strategies may be efficacious in one setting but not another. For example, CD34+ cells are present in both circulating progenitor cells and whole bone marrow mononuclear preparations, mesenchymal stem cells are only present in the bone derived progenitor cell preparations.

Similarly, the literature to date has demonstrated critical differences between myocardial tissue immediately after and that at times remote from an acute ischemic event with respect to the expression of stem cell homing factors, inflammatory infiltrates and putative differentiation factors.5,6,7 Thus, although CD34+ cells may be able to home to myocardial tissue in the perifarct period,5,6 CD34+ cells may require direct injection into the myocardial tissue at times remote from acute myocardial infarction.3,8

Clearly there are numerous technical and biological questions that are yet to be resolved regarding cell based therapies for the prevention and treatment of cardiac dysfunction including optimal cell type, timing of delivery, dosing and the mechanisms of benefit. However, an equally important challenge to the field is determining which patients may benefit from treatment. Identifying patient characteristics that enrich patient populations that benefit from cell therapy will ultimately decrease the size of clinical trials, maximize the benefit-risk ratio to patients for an invasive therapy, potentially offer insight into mechanism, and allow for efficient translation of this novel form of therapy to clinical populations.9

In this issue Assmus and colleagues investigate the clinical and biomarker characteristics of the TOPCARE-CHD that predicted which patients benefited from infusion of bone marrow derived progenitor cells.10 The patient population studied included 121 patients pooled from the randomized portion of the TOPCARE-CHD study as well as a subsequent registry of patients that received bone marrow derived progenitor cells. Of note the crossover design of the randomized TOPCARE-CHD study combined with the fact that circulating progenitor cells were shown to have no effect increased the number of patients available for this analysis. Thus, beyond offering all potential study subjects with heart failure the opportunity for potential benefit, implementation of the crossover study design significantly increases the ability to perform retrospective analyses following completion of the study. Assmus and colleagues first analyzed the clinical characteristics of those patients that, 3 months after cell infusion, were deemed responders as defined by at least a 10% decrease in circulating levels of NT-pro-BN or NT-pro-ANP. Interestingly the findings of this analysis suggest that patients with increased evidence of heart failure, not worse cardiac function, responded to progenitor cell infusion. Focusing on those patients who responded based on NT-pro-BNP, as this marker in general appeared more revealing, those patients that had a 10% decrease in NT-pro-BNP levels had a higher baseline NT-pro-BNP levels (2311 pg/mL versus 876 pg/mL, P=0.03) but a trend toward higher baseline ejection fraction (43% versus 38%, P=0.08). Whether the increased benefit in patients with increased heart failure is because of intrinsic differences in the ability of the myocardium to recruit and engraft the progenitor cells, respond to paracrine signaling or the need is simply greater is unclear and warrants investigation.

An additional predictor of a significant decrease in NT-pro-BNP 3 months after progenitor cell infusion was the functional capacity of the progenitor cell preparation as quantified by colony forming units. On average those patients that responded with a >10% decrease in NT-pro-BNP received a progenitor cell preparation that had ≈37%
greater colony forming unit capacity than those that did not. Not surprisingly these data demonstrate that the more functional and/or viable the cell preparation the more likely the therapy is to yield benefit. Unfortunately, those patients that yielded cells with a low colony forming unit capacity had a trend toward a higher baseline NT-pro-BNP. Thus, the very patients that benefit from progenitor cell infusion are less likely to yield a sufficiently functional bone marrow progenitor cell preparation. This interesting observation raises the proverbial chicken and egg argument, do patients have worse heart failure because of dysfunctional progenitor cell based repair processes, or is the narrow dysfunction secondary to the presence of heart failure? The issue is not simply a matter of patient age, because those patients that were NT-pro-BNP responders tended to be older (63 years versus 59 years, \( P = 0.07 \)). An answer to this question is clearly important to our understanding of the role of progenitor cells in the pathophysiology of left ventricular remodeling and heart failure. As suggested by the Authors strategies for improving progenitor cell function, like increasing eNOS expression, could ultimately be important in improving the response to therapy.\(^{11}\) Another approach could be using immune privileged allogeneic progenitor cells, (ie, mesenchymal stem cells or multipotent adult progenitor cells) from healthy donors.

In this population of 121 patients there were 14 deaths with the longest period of follow-up being approximately 5 years. Although it is difficult to draw conclusions from a study with such a small number of clinical end points, the findings are interesting and demonstrate the critical importance of identifying the right patients and the right cell preparations in order for benefit to be observed. The Authors stratified the survival curves based on whether the patient’s baseline NT-pro-BNP was above or below the median, as well as by whether the patient’s progenitor cell preparation yielded above or below the median number of colony forming units. This analysis demonstrated that there was a significant increase in survival in patients with high baseline NT-pro-BNP levels who received functional progenitor cells compared with patients with high baseline NT-pro-BNP levels who received preparations that yielded a low number of colony forming units. There was only a modest benefit observed in patients that had baseline NT-pro-BNP levels below the median; however, it is noteworthy that there were no deaths observed in patients that had low NT-pro-BNP levels and received preparations with above the median numbers of colony forming units. Although this finding clearly needs to be verified, it potentially raises the bar for future studies not to simply focus on measures of cardiac function and perfusion, but to strive for mortality end points. Unfortunately this study does not teach us as to what mode of demise has been decreased. Recent literature has suggested the engrafment of mesenchymal stem cells can result in a decrease in arrhythmogenic risk that could be translated to decreased sudden death\(^{12}\); however, the decline in NT-pro-BNP suggests that there may have been decreased clinical heart failure in treated patients. Clarifying the mode of demise should be a goal in future trials.

In summary, this retrospective analysis by Assmus and colleagues advances our understanding of the types of patients that should be enrolled in clinical trials testing the effects of cell therapy at a time remote from AMI. It further supports the concept that, although perhaps more difficult to enroll, patients with greater myocardial damage in the case of AMI and more heart failure in the case of ischemic cardiomyopathy are the correct and interesting to study. Finally, these data further demonstrate the importance of quantifying by some measure the functional capacity of the cell preparation so that results can be stratified by both clinical and cellular characteristics.

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References


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