Is Cell Therapy Promising or Lost in Translation in Patients With Acute Myocardial Infarction?

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Conventional therapy for acute myocardial infarction (AMI) is established. However, in some patients, AMI leads to cardiac dysfunction, resulting in an increase in mortality rate. Thus, therapeutic strategies to prevent severe cardiac dysfunction in patients with AMI must be established. Cell therapy is promising for restoration and maintenance of cardiac function in patients with AMI. Results of 10 pilot studies using cell therapy have so far been reported, and more than 20 clinical trials involving patients with AMI and congestive heart failure are ongoing.¹ Unfortunately, not all studies have been equally positive; in some cases, there

were no effects.^{2,3} In addition, the results of some studies using animal models have not supported the efficacy of cell therapy for AMI.^{4,5} Although clinical trials have shown no adverse effects during follow-up periods of 2–18 months, some adverse effects, such as coronary restenosis and arrhythmia, have been described in case reports.^{1,6,7} Controversial results of clinical trials using cell therapy in patients with AMI might be due to different study protocols, including the transplanted cell source, number of cells, cell isolation, cell storage, cell delivery system, timing of cell administration, outcomes, and selection of patients.

Figure. Ideal cell therapy and critical issues that remain to be resolved in acute myocardial infarction.

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In this issue of the Journal, in the study by Turan et al,⁸ the efficacy of an intracoronary administration of autologous freshly isolated bone-marrow mononuclear cells for left ventricular function in patients with AMI was confirmed. The method of cell isolation is one of the critical issues that should be resolved when optimal cell therapy is performed for AMI. It is expected that an increase in activity of isolated cell function and number of isolated cells might have beneficial effects on cardiac function and structure after cell therapy. Interestingly, the system for harvesting bone-marrow autologous cells used in the present study increased the yield of isolated bone-marrow cells compared with the yield obtained from the Ficoll isolation method, and isolated cells obtained by the harvest bone-marrow autologous cell system included much higher numbers of stem or progenitor cells (eg, CD34⁺ and AC133⁺) and platelets than those obtained by using the Ficoll isolation method. Isolation time using the harvest device is relatively short. In addition, the advantage of cell isolation by the harvest bone-marrow system is not needed to require good manufacturing practice. Although fetal calf or bovine serum must be used in cell culture using previous cell isolation protocols, harvested bone-marrow cells are resuspended in the patient's autologous plasma, resulting in prevention of contamination. The harvest bone-marrow technique, rather than the Ficoll technique, might therefore be the best cell isolation system at present.

If we obtain an adequate cell isolation system, we will run head-on into a number of critical issues. **Figure** shows an algorithm for the ideal cell therapy and critical issues that remain to be resolved, including sources of transplanted cells (bone marrow-derived cells, hematopoietic stem cells, mesenchymal stem cells, adipose tissue-derived cells, skeletal myoblasts, and induced pluripotent stem cells, or induced cardiomyocytes and myocardial progenitor cells); sufficient number of transplanted cells; establishment of a cell delivery system (intracoronary, intravenous, and transmyocardial administration, and use of cell sheets); development of new modalities for cell delivery (cell implantation catheter and cell sheets); success of cardiomyogenesis; coexistence of angiogenesis and neurogenesis; and examination of cardiac function and arrhythmia. Another critical issue is that mechanisms by which cell therapy improves cardiac function and structure in patients with AMI remain unclear. It has been shown that transplanted adult stem cells die within 7 days after implantation and do not differentiate into cardiomyocytes in animal models of AMI.^{9,10} Stem or progenitor cells contain various growth factors and cytokines.^{11,12} Results of several studies support the concept that growth factors and cytokines released by implanted cells predominately contribute to the improvement in cardiac function through mobilization of various progenitor cells, including myocardial progenitor cells.^{13,14} However, it is unknown whether these mechanisms work in humans. Further studies are needed to elucidate the precise mechanism of cell therapy-induced improvement in cardiac function in patients with AMI. Finally, attention should be given to the safety of cell therapy, par-

ticularly the risk of ventricular arrhythmia, acceleration of atherosclerosis, and canceration in long-term, follow-up periods. Until these critical issues have been addressed, it is unclear whether cell therapy is promising or lost in translation in patients with AMI.

To reach the complete goal of cell therapy for acute myocardial infarction, we must resolve critical issues and we still have a long way to go. "Rome was not built in a day."

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