Insights From 10-Year Outcomes of Mesenchymal Stem Cell Transplantation in Heart Failure Patients

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The global incidence of chronic heart failure (CHF) is increasing, and it is a leading cause of death worldwide.¹ Although medical and surgical therapies have progressed in recent decades, treatment of CHF patients with severe left ventricular (LV) dysfunction remains limited and the development of innovative methods is still needed.

Cell therapy using mesenchymal stem cells (MSCs) is a novel strategy to recover reduced ejection fraction (EF) and improve the outcome in CHF patients. Preclinical studies have demonstrated favorable effects of MSC therapy on

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cardiac function in rodents.² Since the mid-2000s, clinical trials, including randomized controlled trials (RCTs), using bone marrow-derived MSCs (BMMSCs) have been conducted.³ A meta-analysis of cell therapy studies using bone marrow-derived cells, including BMMSCs (50 studies, 2,625 recipients) demonstrated that patients receiving cell therapy resulted in improvement of LV function with greater EF (+3.96%), reduced infarct size, and smaller LV volume.⁴

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Table. Comparison of Short- and Long-Term Effects of Cell Therapy Between Groups With Low and High Numbers of Transplanted Cells

	Transplanted cell number		P value
	Low group	High group	
Patient no.	2, 4, 8	1, 3, 5, 6	
Cell number ($\times 10^6$)	12 (12, 18)	56 (51, 60)	0.04
Age (years)	60 (58, 65)	41 (35, 49)	0.15
Male sex	2	3	1.00
Etiology			0.49
DCM	1	3	
ICM	2	1	
Change between baseline and 2 months after cell transplantation			
BNP (pg/mL)	+5 (−38, +104)	−20 (−35, −13)	0.86
LVEF (%)	0 (0, +1.5)	+3 (−0.5, +4.3)	0.59
% PVC (%)	−0.1 (−0.2, +0.4)	−0.6 (−0.6, +1.5)	0.80
Peak $\dot{V}O_2$ (mL/min/kg)	+0.4 (−0.1, +0.9)	+1.6 (−0.3, +3.7)	0.53
Change between baseline and 5 years after cell transplantation			
BNP (pg/mL)*	+152 (+116, +189)	−35 (−41, +46)	0.40
LVEF (%)*	−13 (−16, −11)	+2.0 (+1.5, +5.5)	0.20
NYHA class			0.49
Improved	0	0	
Unchanged	1	3	
Worsen or died	2	1	

Numeric values are expressed as median and interquartile range (25th percentile, 75th percentile). *Excludes patient no. 3 (heart transplantation) and patient no. 8 (died). BNP, B-type natriuretic peptide; DCM, dilated cardiomyopathy; ICM, ischemic cardiomyopathy; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PVC, premature ventricular contraction; $\dot{V}O_2$, oxygen uptake. (Reproduced with permission from reference 10.)

Therapeutic Effects of MSCs on HF

MSCs can be isolated from various sites of the body, including bone marrow, adipose tissue, umbilical cord blood, and dental pulp. MSCs have self-renewal potential and paracrine capacities of growth factors such as vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), and fibroblast growth factor (FGF).^{5,6} Furthermore, under appropriate conditions, they can be transdifferentiated into cardiomyocytes (**Figure**). Paracrine effects are the major mechanism of action of MSCs on damaged cardiac resident cells, including endothelial cells, fibroblasts, and cardiomyocytes. Interestingly, MSCs are also reported to inhibit the downregulation of β -adrenoreceptor expression in a HF model.⁷ These favorable effects are assumed to synergistically contribute to improved cardiac function.

Safety of BMMSC Therapy for HF

Intramyocardial injection of MSCs raises some concerns about arrhythmogenicity and tumor formation, regardless of whether the injected MSCs engraft and transdifferentiate into cardiomyocytes. To treat CHF, skeletal myoblasts were first used around the year 2000. In the MAGIC (Myoblast Autologous Grafting in Ischemic Cardiomyopathy) study, the first multicenter, double blind, RCT of myoblast transplantation in patients with LV dysfunction, arrhythmic events of refractory ventricular tachycardia were reported, although LV volumes were significantly decreased in the treatment group.⁸ In contrast, recent trials have shown that BMMSC transplantation did not increase fatal arrhythmias.⁴

Tumor formation is also a major and possible complica-

tion of BMMSC therapy because heart and ectopic tumor formation has been reported in experimental studies.⁹ Fortunately, there is no evidence to date of malignant tumor formation associated with BMMSC transplantation. However, follow-up periods of almost all of the reported studies were up to a maximum of 3 years. Compared with other complications, including hemorrhage, infection and arrhythmia, tumor formation potentially occurs in the later phase after cell therapy. Therefore, a longer survey for tumor formation is required to confirm the safety of MSC therapy. In this issue of the Journal, Yagyu et al¹⁰ report their 10-year outcomes of BMMSC therapy via intramyocardial injection for symptomatic CHF patients (EF <40%, ischemic and non-ischemic). No major adverse events, such as fatal arrhythmia and malignant tumors directly caused by BMMSCs injection, were observed during the follow-up period (median: 8.7 years). Although sample size was relatively small (n=8), this is valuable information for researchers and clinicians involved in cell therapy.

Efficacy of BMMSC Therapy for HF

Importantly, Yagyu et al also investigated the efficacy of cell therapy, particularly the relationship between the changes in EF from baseline values and the number of injected BMMSCs (**Table**). In this analysis, patients received a higher number of BMMSCs (High group, median 56×10^6 cells), demonstrating +3% EF at 5 years after cell therapy. Although this is statistically insignificant because of the small sample size, patients receiving a lower number of BMMSCs (Low group, median 12×10^6 cells) showed progression of LV dysfunction with decreased EF by −13% from baseline. Moreover, the High cell number group also

showed a reduced B-type natriuretic peptide level relative to baseline (High group vs. Low group, -35 vs. $+152$ pg/mL). Consistently, in the CCTR TIME (Cardiovascular Cell Therapy Research Network Timing in Myocardial Infarction Evaluation) trial, administration of a higher percentage of CD45⁺CD31^{low} bone marrow-derived single cells resulted in significantly reduced infarct size at 6 months after cell therapy.¹¹ Recently, several studies have reported that repeated injections of bone marrow-derived cells significantly improve LV function and long-term survival.^{12,13} These data give insights into the improvement of BMMSC therapy, because cell therapy might exhibit dose-dependent efficacy.

In summary, the safety and feasibility of BMMSC therapy for CHF patients has become widely recognized. The 10-year outcomes reported by Yagyu et al provide valuable information regarding long-term safety.¹⁰ The efficacy of current BMMSC therapy is favorable, but still modest.⁴ High-dose or repeated injections of BMMSCs might greatly improve the efficacy of cell therapy. Further investigations and technical/methodological improvements, as well as a well-designed clinical trial, could affirm the clinical application of MSC therapy for CHF treatment.

Conflict of Interest

The authors report no relationships that could be construed as a conflict of interest.

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