Autologous bone marrow stem cell transplantation contributes to exercise capacity recovery after acute myocardial infarction

5th World Congress on
Cell & Stem Cell Research

M. M. Micheu, N. Oprescu, L. Calmac, D. Pitic, A. Scarlatescu, M. Dorobantu

Department of Cardiology, Clinical Emergency Hospital of Bucharest, Romania

Introduction and objective

In spite of latest treatment, acute myocardial infarction is still a major cause of mortality and morbidity worldwide. The brutal injury of myocardium leads to a sudden increase of loading conditions and initiates a process of unfavorable ventricular remodeling, which affects not only the necrotic muscle, but the border zone and the distant myocardium as well (McKay et al., 1986). This evolving process leads to gradual dilatation, recruitment of border zone myocardium into the scar and decline of contractile function. As a result, heart failure occurs, with all its consequences (Pfeffer et al., 1990). Although standard-of-care drug therapy (e.g., with beta-receptor blockers and/or angiotensin-converting enzyme inhibitors) may delay remodeling process, there is no basic therapeutic regimen available for preventing or even reversing this evolution. By the use of interventional therapeutics (percutaneous transluminal coronary angioplasty), recanalization of the occluded infarct-related artery is possible, thus improving or normalizing the coronary blood flow. However, even with sufficient reperfusion of infarcted tissue, the viability of the infarcted myocardium cannot, or can only insufficiently, be improved in most of these patients. Therefore, catheter-based therapy of acute myocardial infarction is useful for vascular recanalization, but the second and crucial step, the regeneration of necrotic heart muscle, is not realized by this vascular procedure alone.

As the heart has only a very low potential for repair and regeneration, the ability of pharmacological agents to improve cardiac function is limited as these agents do not address the fundamental issue of cell loss. This has led to the search for a new approach in the treatment of patients with myocardial infarction.

The discovery made by Asahara and colleagues (1999) that postnatal vasculogenesis exists, provided new insights into mechanisms of cardiac repair. These data, as well as the original work of Orlic and collaborators (2001) that showed improved cardiac function in a mouse model of myocardial ischemia, in which grafted cells were seen in the infarcted region and differentiated into cardiomyocytes, are the basis of bone marrow stem cells use in ischemic cardiac disease.

Stem cell (SC) therapy intends to regenerate structurally and functionally the injured heart by preventing and improving the cardiac remodeling; this innovative therapy is used additional to current guidelines recommendations.

Methods

This pilot study was conducted on 18 patients hospitalized for a first STEMI treated by successful primary percutaneous coronary intervention (PCI) and LVEF < 40%.

Table #1 1 Baseline characteristics

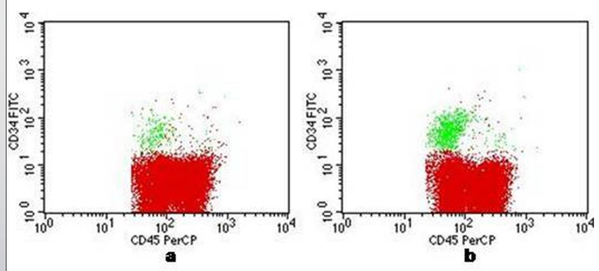
Variables	ABMSC group N = 7	Control group N = 11	p
Age - years mean ± SD	58.57 ± 8.69	55.91 ± 15.53	NS
BMI - kg/m2 mean ± SD	29.4 ± 4.73	24.24 ± 3.02	0.01
Sex			
•M	6 (85.7%)	8 (72.7%)	NS
•F	1 (14.3%)	3 (27.3%)	
Smoking			
•Yes	4 (57.1%)	9 (81.8%)	NS
•No	3 (42.9%)	2 (18.2%)	
Diabetes mellitus			
•No	6 (85.7%)	9 (81.8%)	NS
•Yes	1 14.3(%)	2 (18.2%)	
Dyslipidemia			
•No	3 (42.9%)	6 (54.5%)	NS
•Yes	4 (57.1%)	5 (45.5%)	
Hypertension			
•No	3 (42.9%)	4 (36.3%)	NS
•Yes	4 (57.1%)	7 (63.7%)	
Time from pain onset to PCI (hours)	11 ± 1.73	8 ± 3.51	NS
Diseased coronary arteries n (%)			
•1	4 (57.1%)	2 (18.2%)	
•2	2 (28.5%)	6 (54.5%)	NS
•3	1 (14.3%)	3 (27.3%)	
Preprocedural TIMI flow n (%)			
•TIMI 0	6 (85.7%)	8 (72.7%)	
•TIMI 2	1(14.3%)	2 (18.2%)	NS
•TIMI 3	0 (0%)	1 (9.1%)	
Postprocedural TIMI flow n (%)			
•TIMI 0	1 (14.3%)	0 (0%)	
•TIMI 2	0 (0%)	3 (27.2%)	NS
•TIMI 3	6 (85.7%)	8 (72.8%)	
LVEF-2D %	29.87 ± 2.83	30.45 ± 5.18	NS

All the patients have received the standard of care treatment, and were followed-up using the same methods, comprising 6-minute walking test with assessment of heart rate, blood pressure and Borg Scale before and after the test, 1 and 3 months after STEMI.

In the ABMSC group, 50 ml of bone marrow were harvested 7 to 13 days after PCI. After density gradient separation, the mononuclear bone marrow cell suspension was delivered via intracoronary route in the catheterization laboratory during the same day.

Figure #1

Flow cytometry aspect of bone marrow cell suspension before (a) and after density gradient separation respectively (b). The CD45+ cells are represented in red, while the CD34+ cells are represented in green.



Results

There were no adverse effects related to stem cell therapy during 3 months follow-up period. In stem cells treated group, the 6-minute walk distance increased significantly (from 271.14 ± 99.92 m at one month follow-up to 311.57 ± 79.83 m at 3 months after myocardial infarction, P < 0.05), while in control group the improvement didn't reach the limit of statistical significance (297.18 ± 71.71 m to 330.83 ± 47.94, P > 0.05).

Conclusions and future directions

We observed a positive effect of autologous bone marrow stem cell therapy in STEMI patients with severe systolic function impairment regarding exercise capacity. Larger studies are required in order to reveal the intimate mechanisms of action and the real magnitude of this favorable effect.

Still, in order to use stem cells as a current therapeutic method in clinical practice, a number of problems should be solved first:

- Developing new effective strategies to stimulate migration, engrafting and cell survival;
- Determining the relationship between the active effect (contraction stimulation) and passive effect (remodeling inhibition) from quantitative and also temporal perspective;
- Personalizing cell therapy according to individual patient characteristics - including age and associated comorbidities.

Bibliography

1. McKay RG, Pfeffer MA, Pasternak RC, et al. Left ventricular remodelling after myocardial infarction: a corollary to infarct expansion. Circulation 74:693–702, 1986.
2. Pfeffer MA, Braunwald E. Ventricular remodelling after myocardial infarction. Experimental observations and clinical implications. Circulation 81:1161–72, 1990.
3. Asahara T, Masuda H, Takahashi T, Kalka C, Pastore C, Silver M, Kearne M, Magner M, Isner JM. Bone marrow origin of endothelial progenitor cells responsible for postnatal vasculogenesis in physiological and pathological neovascularization. Circ Res.85:221–228, 1999
4. Orlic D, Kajstura J, Chimenti S, Jakoniuk I, Anderson SM, Li B, Pickel J, McKay R, Nadal-Ginard B, Bodine DM, Leri A, Anversa P. Bone marrow cells regenerate infarcted myocardium. Nature 410 (6829): 701–5, 2001.

Acknowledgement

This paper is supported by the Sectoral Operational Programme Human Resources Development (SOP HRD), financed from the European Social Fund and by the Romanian Government under the contract number POSDRU/159/1.5/S/137390.