The Pharma Innovation Journal 2018; 7(1): 384-388

www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating: 5.03
TPI 2018; 7(1): 384-388

www.thepharmajournal.com
Received: 15-11-2017
Accepted: 19-12-2017

Artur Gabriyelyan
Department of Cardiac Surgery and Transplantation, The National Institute of Surgery and Transplantology, Kyiv, Ukraine

Correspondence
Artur Gabriyelyan
Department of Cardiac Surgery and Transplantation, The National Institute of Surgery and Transplantology, Kyiv, Ukraine

Left ventricular 2D speckle tracking echocardiography, quality of life and annual mortality in patients with dilated cardiomyopathy from cardiac transplant waiting list

Artur Gabriyelyan

Abstract
For patients with dilated cardiomyopathy drug therapy is often ineffective and heart transplantation remains the single radical but the most efficient method of treatment. At the same time, investigators suggest that the stem cell transplantation (SCT) can be a promising palliative concept for this group of the patients.
The aim of research was to study the data of left ventricular 2d speckle tracking echocardiography, quality of life and annual mortality in patients with dilated cardiomyopathy in pharmacological treatment versus stem cell transplantation.
A total 40 people were involved in the study - group 1 - conservative treatment (20 patients); group 2 (20 patients), where transplantation of cord stem cells was used. At the beginning of the study, clinical data and physical investigation were analyzed. Examinations included ECG, cardiac ultrasound techniques, strain rate imaging and N-terminal pro brain natriuretic peptide was provided.
It was proved, that in patients from cardiac transplant waiting list with dilated cardiomyopathy stem cell therapy promotes a significant increase of left ventricular ejection fraction, parameters of systolic (S, ν, p<0,05) and diastolic (e, a, p<0,05), longitudinal (p<0,05), transmural (p<0,05) and circular (p<0,05) strain rate imaging versus conservative therapy. It was set improvement both physical (p<0,05) and mental (p<0,05) health by Minnesota survey in the group of DCM from cardiac transplant waiting list, where transplantation of umbilical cord blood stem cells was used in compare to conservative treatment. Cardiovascular and total mortality relative risk became 15,0% reduced after the use of stem cells transplantation against conservative treatment.
The results obtained in the research allowed to propose a procedure of stem cell transplantation for the treatment of left ventricle systolic dysfunction in patients with DCM from cardiac transplant waiting list.

Keywords: Stem cells transplantation, heart failure, dilated cardiomyopathy, cardiac transplant waiting list

1. Introduction
Heart diseases take the main position in structure of world population morbidity and mortality. However, chronic heart failure (HF) is the mandatory component of the final stage of the major part of cardiovascular diseases. On the other hand, HF is often considered as additional concomitant diagnosis to the main cardiac disease.
A significant role among non-coronary heart diseases with concomitant HF has dilated cardiomyopathy (DCM) [4]. For patients with DCM drug therapy is often ineffective [7]. Nowadays heart transplantation (HT) remains the single radical but the most efficient method of treatment of DCM [2].
Overall, some alternative methods, which may extend the survival lifetime and increase life quality of patients with DCM are permanently being learnt. Certain investigators suggest that the stem cell transplantation (SCT) can be a promising palliative concept for this group of the patients [5, 6].
In TOPCARE-CHDB trial [3] was set the significant improvement of left ventricle (LV) function after SCT. However, in other studies has demonstrated that SCT is associated with a constant level of adverse effects [1, 9].
Therefore, the management of patients with dilated cardiomyopathy in cardiac transplant waiting list remains an important problem of cardiology.
The purpose our research was to study the data of left ventricular 2d speckle tracking echocardiography, quality of life and annual mortality in patients with dilated cardiomyopathy in pharmacological treatment versus stem cell transplantation.

2. Materials and methods

2.1 Clinical characteristics of the patients

40 people were involved in the investigation with the diagnosis of heart failure due to dilated cardiomyopathy from the waiting list on heart transplantation. Two groups were distinguished, depending on the method of treatment: group 1 - group, which received only conservative treatment (20 patients); group 2 (20 patients), where transplantation of cord stem cells was used [8].

The inclusion criteria were a patient written consent the participation in the study, patients with III-IV functional class of HF by NYHA and the presence of systolic dysfunction of the left ventricle (ejection fraction (EF) less than 40,0%). The average age of patients was 49,7±12,3 years.

After SC-transplantations general condition and cardiac hemodynamic of patients was monitored at the intensive care departments by means of module monitor DRAGER Infinity Gamma XL (Drager Medical AG & Co, Germany) within 2 hours.

Complaints, general physical status and efficiency of the treatment were controlled during the day of admission to hospital, early period (the 7th day), late period (the 30th day), and every 3 month during 12 month period.

2.2 Clinical methods

At the beginning of the study, clinical data (complaints, anamnesis data, and physical investigation were analyzed). Instrumental examinations included ECG, cardiac ultrasound techniques, ventriculography. In addition, laboratory findings were analyzed and immunoassay analysis by measuring the content of N-terminal pro brain natriuretic peptide (NTproBNP) was provided.

HF and its functional class was verified on the basis of criteria of 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. The quality of life was estimated according to Minnesota Living with Heart Failure Questionnaire.

2.3 Clinical research methods

Measuring of concentrations of N-terminal pro brain natriuretic peptide (NTproBNP) was performed by immunoassay testing (IAT) on the Rayto-2100C immunoassay analyzer (China).

Holter daily monitoring was made in 3 modifying precordial leads.

Echocardiography was performed in horizontal position of a patient on the back or on the left side in the second-third-fourth intercostal space using M-, B- regimens, in wave-impulse and wave-color Dopplerography by means of standardize methods using the sectoral sensor with the frequency of 2,5-5,0 MHc.

After standard echocardiography and Dopplerography, Strain Rate Imaging was made for all the patients. The sector of ultrasound investigation was chosen on the base of the rule that external contour of the left ventricle never crosses the borders of ultrasound window. The ultrasound loop was recorded by three circles of cardiac contractility in B-regimen. Then, using software «Wall Motion Tracking» (WMT) with option «4Ch Tracking» the best circle of contractility was defined and external and internal end-diastolic border of LV was fixed. The indices and other results of echocardiography were calculated and saved in special software

2.4 Stem cell transplantation

The biological preparation "Cryopreserved cord human blood" was prepared at the «Institution of Cell Therapy» (Kyiv, Ukraine). This cell preparation contains stem cells and blood haemopoietic cells. The cell concentration was the following: the mean general quantity - from $0,890*10^9$ till $0,950*10^9$; the concentration of mononuclear cells - from $0,486*10^9$ till $0,520*10^9$ and CD34+ type cells – non less than $1,0±0,01*10^9$/ml.

2.5 Statistical methods

Statistica for Windows version 10.0 (Stat Soft inc., USA) and WinPepi software version 11.62 were used for statistical analysis of the obtained results.

3. Results and Discussion

3.1 Echocardiography and Strain Rate Imaging

After 6 months LV ejection fraction (EF) in the group of conservative therapy decreased from 28,5±4,12% to 26,4±3,78% (p>0,05), in one year to 25,8±2,78% (p<0,05). In the group 2 (stem cell therapy) was set the increase of LV EF after 6 months (from 27,5±2,34% to 33,5±2,14%, p<0,05), and to 34,9±2,76 after 12 months (p<0,05).

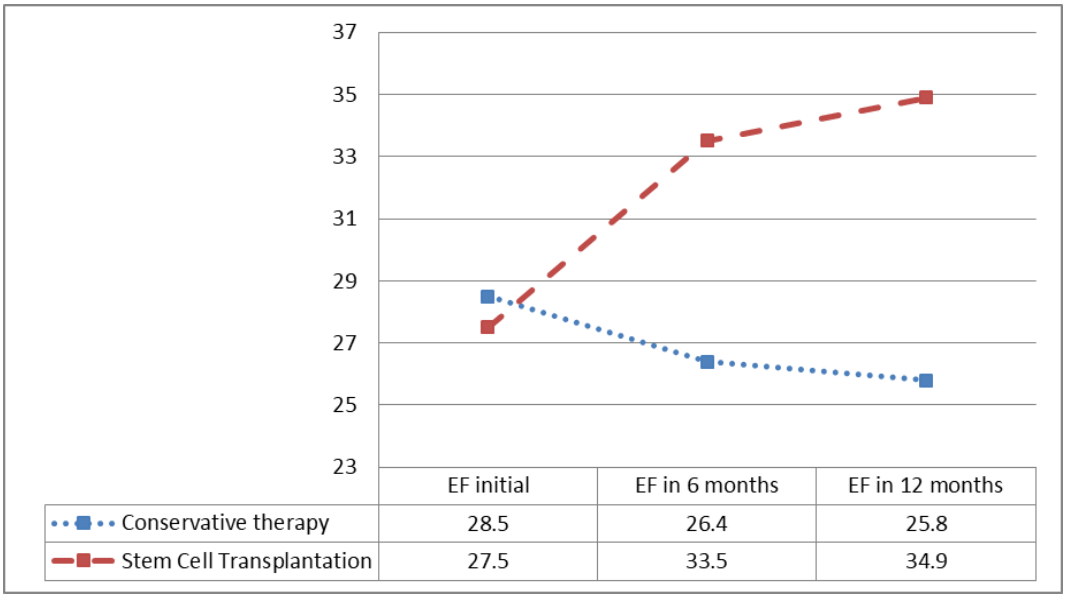

Fig 1: Ejection fraction of the left ventricle at different treatment regimens in patients with DCM in the cardiac transplant waiting list.

Data of Strain Rate Imaging in patients with DCM are shown in Table 1. It was established that after SCT, the parameters of the systolic (S, ν) and diastolic (e, a) functions of the left ventricle are reliably improved, whereas the use of conservative therapy were unlikely, and in some cases, it was set the worsening of local contractility.

Table 1: Indices of local contractility of the left ventricle under different treatment regimens in patients with dilated cardiomyopathy

	Conservative therapy		Stem Cell Transplantation	
	Initial	**In 12 months**	**Initial**	**In 12 months**
EMK	6,74±1,18	6,62±1,67	6,58±0,59	7,16±0,72*
s'	7,72±1,19	7,54±1,76	7,11±0,18	8,21±0,23*
e'	7,75±1,12	7,74±1,48	7,58±0,62	8,14±0,72*
a'	6,56±1,62	6,32±1,61*	6,21±0,43	6,91±0,61*
e'/a'	1,65±0,49	1,79±0,58*	1,59±0,37	1,34±0,17*
E/e'	8,82±1,54	8,35±1,0*	8,59±1,43	7,24±1,19*
S_L	4,39±1,67	4,17±1,34	4,12±0,32	4,78±0,41*
S_{T1}	3,98±2,12	3,65±2,37	3,56±0,31	4,34±0,18*
S_{L2}	3,92±1,23	3,83±1,45	4,08±0,51	4,44±0,44*
S_{T2}	3,87±1,29	3,67±1,51	3,52±0,34	3,93±0,24*
$ν_{L1}$	2,28±0,69	2,04±0,87	2,54±0,28	2,93±0,27*
$ν_{L2}$	1,82±0,59	1,71±0,64	1,84±0,22	2,20±0,54*
$ν_{T1}$	1,64±0,51	1,49±0,79	1,74±0,26	2,18±0,54*
$ν_{T2}$	1,61±0,89	1,52±0,34	1,54±0,21	1,89±0,14*

Note: EMR - excursion of the mitral ring; SL1 - longitudinal peak systolic shift of basal segments, calculated as arithmetic mean when rendered; SL2 - longitudinal peak systolic shift of basal segments derived from global graphics; ST - longitudinal transmural shift of basal segments ν - left ventricular myocardial velocity; νL - longitudinal peak-systolic velocity of basal segments; νL1 - longitudinal peak-systolic velocity of basal segments, calculated as arithmetic mean when rendered; νL2 - longitudinal peak-systolic velocity of basal segments, derived from the global graph of the indicator; νT - longitudinal peak-systolic velocity of basal segments.
* - significant changes after treatment.

3.2 Specific complications after transplantation of umbilical cord blood stem cells.

At the next step was studied the specific complications after transplantation of umbilical cord blood stem cells. In order to study the peculiarities of cardiac rhythm in patients with HF and detecting a possible negative effect of stem cells on the electrophysiological processes in the myocardium, all patients provided daily Holter-ECG monitoring for a specified period (before stem cells transplantation, at the end of 1, 3, 6 and 12 months). The dynamics of the ventricular extrasystoles in the post-transplantation period is given in Table 2.

Table 2: Changes of developing ventricular extrasystoles after stem cells transplantation in patients with dilated cardiomyopathy

Class Lown-Wolf	Before transplantation n=20		1 month n=20		3 months n=20		6 months n=19		12 months n=17	
	Abs.	**%**	**Abs.**	**%**	**Abs.**	**%**	**Abs.**	**%**	**Abs.**	**%**
I	-	-	-	-	8	40,0	7	36,8	5	29,4
II	-	-	2	10,0	2	10,	6	31,6	4	23,5
III	3	15,0	3	15,0	4	20,0	1	5,3	3	17,6
IVa	8	40,0	10	50,0	3	15,0	2	10,5	3	17,6
IVb	9	45,0	5	25,0	2	10,0	2	10,5	2	11,9
V	-	-	-	-	1	5,0	1	5,3	-	-

Comparing the probability of high classes of ventricular extrasystoles among groups, the data given in Table 3 were obtained.

Table 3: Probability of Lown-Wolf Ventricle Extrasystoles in Patients with DCM Depending on Treatment Method

	$N_{patients}$	$N_{rythm\ worsening}$	AE,%	OR	Cumulative Odds Ratio [CI%95]
Conservative therapy	20	8	40,0	1,0	0, 318 [0, 11-0, 87]
Stem Cell Transplantation	20	2	10,0	0,16	
χ^2 – 4,61 (p=0,034)					

So, it was proved, that Stem Cell Transplantation did not increase the risk of Ventricle Extrasystoles high Classes. However, the presence of DCM could have proarrhythmogenic effect for the patients.

3.3 Quality of life

The data of Minnesota survey and quality of life in different methods are presented in Fig. 2.

The conservative therapy did not reduce the restriction of physical and social activity in patients with DCM after 12 months of prospective observation. The usage of SCT had a therapeutic efficacy in 80,0% cases vs. conservative therapy (χ^2=29,98, p<0,001).

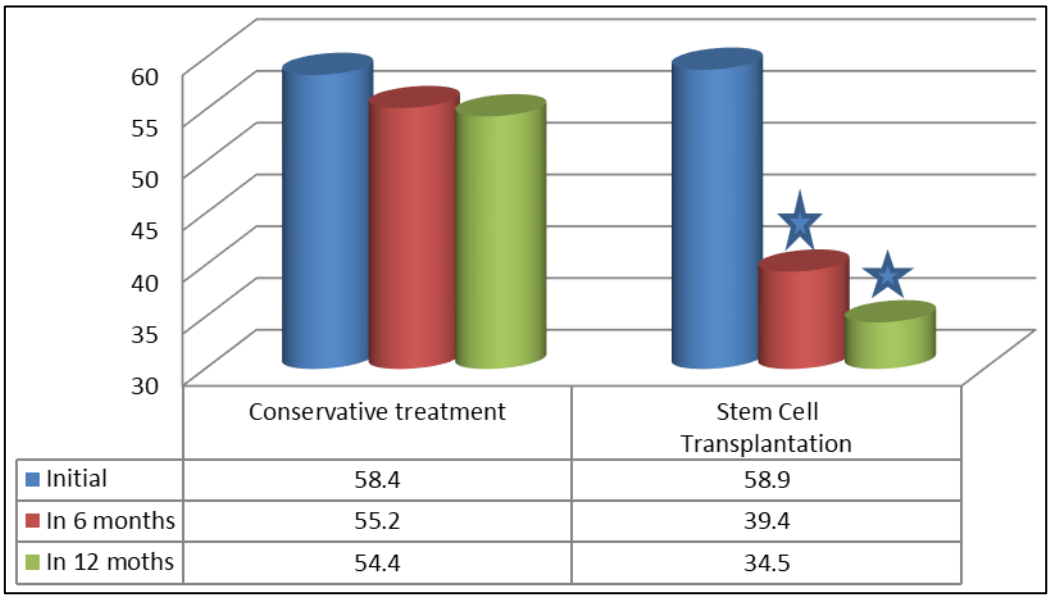

Fig 2: Quality of Life for Minnesota Survey in Patients with DCM.
★-reliable differences in dynamics of treatment (p<0,05).

3.4 NPproBNP level

The initial level of NPproBNP in DCM before treatment was 1219,0±382,4 pg/ml. In 12 months after the transplantation was detected the probable decrease of NPproBNP to 575,6 (293,0-718,0) pg/ml, Fig. 3.

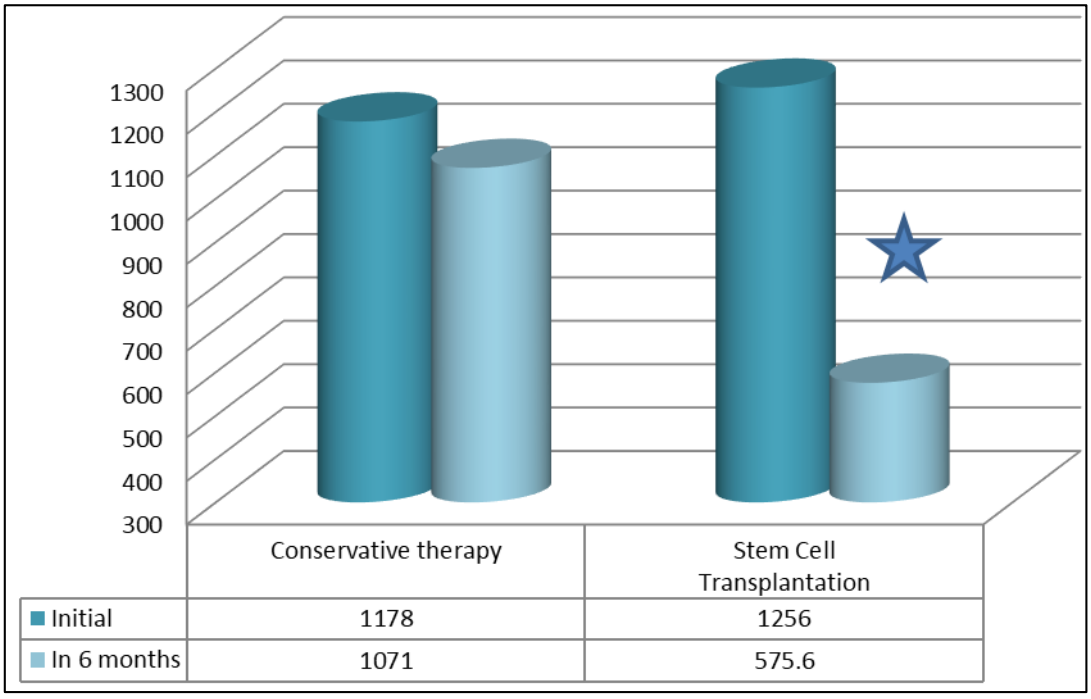

Fig 3: NPproBNP level in patients with DCM in 12 months after treatment.
★- probability of difference of indicators in the dynamics of treatment (p<0,05).

Compared with the groups where conservative treatment were performed, on the background of stem cell transplantation was obtained better efficacy in NPproBNP level (Fig. 3) and absolute efficiency (Table 4).

There was no decrease in NPproBNP level to 50,0% from initial in conservative therapy, and in group 2 at 40,0% patients. So, stem cell transplantation was probably more effective vs. pharmacological method.

Table 4: The probability of decreasing the NPproBNP level to 50.0% in patients with DCM depending on the treatment

	N patients	Decrease NPproBNP 50,0%	AE,%	OR	p
Conservative therapy	20	0	0,0	0,0	$\chi 2$ – 31,4 (p=0,001)
Stem Cell Transplantation	20	14	70,0	44,6	

3.5 Mortality and survival

The risk of cardiac mortality in dilated cardiomyopathy in observational groups is presented in Table 5.

Table 5: Cardiovascular mortality in patients with dilated cardiomyopathy in cardiac transplant waiting list

	AR,%	RR	OR
Conservative therapy	30, 0	2, 0 [0, 97-6, 92]	2, 43 [1, 01-11, 5]
Stem Cell Transplantation	15, 0		

After 12 months of observation, the absolute risk of cardiovascular mortality was 30,0% in group 1 (conservative therapy) and 15,0% in group 2 (SCT). So, after stem cell transplantation the mortality was lower in 15,0% vs. conservative treatment.

4. Conclusions

In patients from cardiac transplant waiting list with dilated cardiomyopathy stem cell therapy promotes a significant increase of left ventricular ejection fraction, parameters of systolic (S, ν, p<0,05) and diastolic (e, a, p<0,05), longitudinal (p<0,05), transmural (p<0,05) and circular (p<0,05) strain rate imaging versus pharmacological therapy.

It was set improvement both physical (p<0,05) and mental (p<0,05) health by Minnesota survey in the group of DCM from cardiac transplant waiting list, where transplantation of umbilical cord blood stem cells was used in compare to conservative treatment.

Cardiovascular and total mortality relative risk became 15,0% reduced after the use of stem cells transplantation against conservative treatment, and by 40,0% as compared with Batista procedure.

The results obtained in the research allowed to propose a procedure of stem cell transplantation for the treatment of left ventricle systolic dysfunction in patients with DCM from cardiac transplant waiting list.

5. References

1. Abou-Saleh H, Zouein FA, El-Yazbi A *et al*. The march of pluripotent stem cells in cardiovascular regenerative medicine. Stem Cell Res Ther. 2018; 9(1):201.
2. Acquatella H. Dilated cardiomyopathy: recent advances and current treatment. Rev. Esp. Cardiol. 2000; 53(1):19-27.
3. Assmus B. Transcoronary transplantation of functionally competent bmcs is associated with a decrease in natriuretic peptide serum levels and improved survival of patients with chronic postinfarction heart failure: Results of the Topcare-CHD registry. Circ. Res. 2007; 100:1234-1241.
4. Klotz S, Loeher A, Drees G, Scheld HH. Surgical therapy of end-stage heart failure. State of the art. Herz. 2006; 31(5):445-54.
5. Lancaster JJ, Koevary JW, Chinyere IR, Goldman S. The Promise of Induced Pluripotent Stem Cell-Derived Cardiomyocytes to Treat Heart Failure. Circ Heart Fail. 2018; 11(10):e005425.
6. Miyagawa S, Sawa Y. Building a new strategy for treating heart failure using Induced Pluripotent Stem Cells. J Cardiol. 2018; 72(6):445-448.
7. Nicolini F, Gherli T. Alternatives to transplantation in the surgical therapy for heart failure // European Journal of Cardio Thoracic Surgery. 2009; 35(2):214-228.
8. Ponikowski P, Voors AA, Anker SD *et al*. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Eur. Heart Jour. 2016; 37:2129-2200.
9. Schick R, Mekies LN, Shemer Y *et al*. Functional abnormalities in induced Pluripotent Stem Cell-derived cardiomyocytes generated from titin-mutated patients with dilated cardiomyopathy. PLoS One. 2018; 17;13(10):e0205719.