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Autologous Mesenchymal Stem Cell Transplantation for the Treatment of Chronic Heart Failure in Dilated Cardiomyopathy: A Clinical Case

Abstract

Dilated cardiomyopathy (DCMP) occupies a significant place among non-coronary heart diseases leading to chronic heart failure (CHF). Due to the high mortality rate associated with DCMP, there is a continuous search for alternative heart-preserving treatment methods as “bridges” to heart transplantation. One of the promising approaches is stem cell therapy.

Aim. To describe our own successful case of intravenous transplantation of autologous mesenchymal stem cells (MSCs) as a palliative treatment for CHF associated with DCMP.

A clinical case. A 48-year-old man with DCMP underwent specialized medical treatment for CHF (stage C) in the cardiology department of the Kharkiv Regional Cardiology Centre. The treatment was supplemented by a double intravenous administration of autologous MSCs, with a one-month interval between the two procedures. The first injection, performed against the background of acute left ventricular failure (ALVF), contained 6 million MSCs, while the second administration involved 4 million MSCs. To assess the patient’s clinical status and heart function, physical examination, electrocardiography, and echocardiography were performed at the time of each injection and one month after each procedure. No adverse reactions or side effects were observed following either procedure.

Discussion. Instrumental evaluation demonstrated that the double intravenous administration of MSCs led to a gradual improvement in overall left ventricular contractility, a progressive reduction in both systolic and diastolic left ventricular volumes, a decrease in left atrial volume, and regression of mitral regurgitation severity from grade II to grade I. Additionally, it contributed to the complete elimination of persistent ventricular extrasystole.

These functional improvements alleviated CHF symptoms (from stage C to stage B), prevented further episodes of ALVF, reduced the need for diuretics, and increased the patient’s tolerance to physical exertion. Positive dynamics in the patient’s clinical condition and echocardiographic parameters were observed as early as one month after each MSC administration.

Conclusions. The intravenous administration of autologous MSCs improves the systolic function of the affected heart muscle and can be considered a promising palliative therapy as part of the comprehensive treatment of CHF associated with DCMP. However, the methodology of its clinical application requires further investigation.

Keywords: stem cell therapy, systolic dysfunction, alternative heart-preserving treatment, “bridge” to heart transplantation, palliative treatment.

Introduction. Dilated cardiomyopathy (DCMP) is the most common type of cardiomyopathy (CMP) and occupies a significant place among non-coronary heart diseases leading to chronic heart failure (CHF). The proportion of non-ischemic cardiomyopathy has increased in recent years [1]. According to autopsy data, 3.7% of all deaths from cardiovascular disease are caused by various types of CMP, with DCMP accounting for 60% of these cases [2]. The prognosis for patients with DCMP remains unfavourable: most die within the first three years of symptom onset, and an additional 4–10% die annually due to disease progression [3]. Given its high mortality rate, DCMP is currently the leading indication for heart transplantation.

Briefly summarizing the etiopathological mechanisms of DCMP, its morphogenesis is primarily based on widespread, irreversible damage to cardiomyocytes, which is likely associated with autoimmune reactions triggered by viral infections [4]. The progressive destruction of myocardial cells leads to decreased energy supply, creating conditions for contractile myocardial cell atrophy. Additionally, secondary circulatory disorders may cause focal ischemic alterations in the myocardium [5].

Myocardial damage results in cardiovascular dysfunction, characterized by marked dilation of both ventricular cavities in diastole to prevent a critical drop in cardiac output, stretching of the fibrous rings of the atrioventricular valves and their relative insufficiency, a significant increase in end-diastolic ventricular filling pressure, blood stasis in both circulatory systems, the development of passive pulmonary hypertension, and venous blood congestion in the liver and other abdominal organs [6].

Thus, in DCMP, myocardial pumping dysfunction leading to CHF is primarily due to a decrease in cardiac output and contractility of the damaged myocardium.

In most cases, the radical elimination of the cause of DCMP is impossible, necessitating continuous, lifelong treatment of patients with associated CHF. Pharmacotherapy, along with targeted lifestyle modifications, is the primary treatment approach for CHF, as it can influence the pathophysiological mechanisms of CHF progression and sudden cardiac death, thereby reducing the mortality rate in these patients by up to 6–10% per year [7]. However, modern drug therapy remains ineffective in completely preventing fatal complications in patients with DCMP [8].

At the same time, available organ-preserving surgical methods also have significant limitations, as they do not eliminate the underlying cause of clinically manifested CHF [9]. The most common among them is the Batista procedure, which involves reducing the left ventricular cavity through partial ventriculectomy. It has been established that in some cases, this procedure improves cardiac contractility and helps restore its pumping function. However, due to the high postoperative mortality rate, the ACC/AHA Task Force and the European Society of Cardiology do not recommend this operation because

of its low effectiveness and consider it only as a “bridge” to heart transplantation [10].

Orthotopic heart transplantation remains the only radical surgical treatment for patients in the terminal stage of CHF, including those with DCMP [11]. Following heart transplantation, the survival rate for patients with DCMP is 70% at one year, 48% at five years, and 20.8% at ten years [12].

Therefore, to prolong the life expectancy of patients with DCMP, there is a constant search worldwide for alternative heart-preserving methods of treatment aimed at restoring cardiac contractility or maintaining adequate blood circulation. Among them is resynchronization therapy or the use of various auxiliary devices for circulatory support. A promising palliative direction in the treatment of the refractory stage of CHF is cell therapy.

It has been shown that stem cells (SCs), due to trans-differentiation, cause active regeneration of the damaged myocardium and can stimulate neoangiogenesis [13,14]. Autologous mesenchymal stem cells (MSCs) favourably differ in their immunosuppressive and immunomodulatory properties, inhibiting the recipient’s immune response. These properties make MSCs a candidate for universal cell therapy [15].

Aim. To describe own successful case of performing autologous mesenchymal stem cell transplantation for the treatment of chronic heart failure in dilated cardiomyopathy.

A clinical case. A 48-year-old military serviceman was admitted to the cardiology department in serious condition with complaints of chest pain, rapid heartbeat, general weakness, moist rales, and dizziness. He was transferred from the urology department, where he had been undergoing evaluation for a kidney infarction due to thrombosis of the left renal artery. The above-mentioned symptoms had been present since 2016 and had progressively worsened despite prescribed conservative therapy. No previous medical documentation was provided.

Physical examination revealed shortness of breath during exertion, cough while lying down, general weakness, and pallor of the skin; no swelling was observed. His weight was 100 kg, height 195 cm, temperature (T) 36.6°C, heart rate (HR) 76 beats per minute, blood pressure (BP) 140/85 mm Hg, respiratory rate (RR) 24 breaths per minute, and oxygen saturation (OS) 92% while breathing ambient air. Upon auscultation of the lungs, moist rales were detected, and upon auscultation of the heart, an additional third heart sound was noted. Palpation of the abdomen revealed hepatomegaly, with no signs of ascites. Paster-nacki’s symptom was positive on the left.

X-ray examination of the chest cavity organs: the lung pattern is deformed, the lung roots have increased intensity due to the vascular component.

Electrocardiography (ECG): sinus rhythm, regular, with a frequency of 75 beats per minute, without focal changes.

Ultrasound examination of the heart (EchoCG): the ejection fraction of left ventricle (LV EF) is 24%; the end-diastolic size of the left ventricle (LV EDS) is 7.6 cm; the end-systolic size of the left ventricle (LV ESS) is 6.9 cm; the end-diastolic volume of the left ventricle (LV EDV) is 300 ml; the end-systolic volume of the left ventricle (LV ESV) is 228 ml; stroke volume of the left ventricle (LV SV) is 72 ml; thickness of the interventricular septum (TIS) is 0.91 cm; thickness of the posterior wall of the left ventricle (TPWL) is 1.11 cm; II degree mitral valve insufficiency; systolic pressure in the right ventricle (RV SP) is 30 mm Hg; sizes of the left atrium (LAS) are 6.5[^]5.5 cm; volume of the left atrium (LAV) is 95 ml; aortic diameter (AD) is 2.2 cm and there are traces of effusion in the pleural cavity on the left.

Coronary angiography (CA): the coronary arteries show no hemodynamically significant disorders.

Selective angiography of the left renal artery: signs of mural thrombi.

Multislice computed tomography (MCT): signs of left renal artery thrombosis, left kidney infarction; cardiomegaly; hepatomegaly.

Doppler imaging of the aorta and its branches: occlusion of two branches of the trifurcation of the left renal artery; hemodynamically insignificant kinking of the right renal artery.

D-dimer 201.25 ng/ml (reference values < 243 ng/ml).

The main diagnosis was established as: "Dilated cardiomyopathy; heart failure, class C, with a reduced left ventricular ejection fraction (24%)." The associated diagnosis was: "Left renal artery thrombosis and focal infarction of the left kidney".

Treatment was carried out: carvedilol – 6.25 mg 2 times a day; sacubitril/valsartan – 50 mg 2 times a day; empagliflozin – 10 mg; apixaban – 5 mg 2 times a day; torasemide – 10 mg a day intravenously; heparin – intravenous infusion.

On the 12th day after hospitalization, he was discharged with some improvement in his condition. A heart transplant was recommended. However, in the evening of the same day, the patient's condition worsened: shortness of breath and general weakness increased, and rapid, irregular heartbeat appeared. Upon readmission to the cardiology department, the patient's condition was severe, with a BP of 90/60 mm Hg, an HR of 110 beats per minute, an RR of 28 breaths per minute, and an OS of 86% while breathing ambient air.

ECG: sinus tachycardia, signs of diffuse repolarization disorders.

Daily ECG monitoring (Holter): 6,000 ventricular extrasystoles of two morphologies were detected, including 51 episodes of bigeminy, 53 of trigeminy, 70 paired, and 3 triplet episodes; no pauses longer than 2.5 seconds were registered.

EchoCG: dilatation of all heart cavities, hypokinesia on the back wall of the left ventricle and the interventricular

septum; LV EF – 25%; LV EDS – 7.6 cm; LV ESS – 6.9 cm; LV EDV – 305 ml; LV ESV – 227 ml; LV SV – 78 ml; TIS – 0.91 cm; TPWL – 1.11 cm; II degree mitral valve insufficiency; RV SP – 30 mm Hg; LAS – 6.5[^]6.0 cm; LAV – 105 ml; no traces of effusion in both pleural cavities.

A clinical diagnosis was established: "Dilated cardiomyopathy; mitral valve insufficiency of the II degree; ventricular extrasystolic arrhythmia, class IV A according to Lown; heart failure of the C degree with reduced ejection fraction of the left ventricle (25%); a functional class III (NYHA); acute left ventricular failure".

The patient was intravenously injected with 6,000,000 autologous MSCs. No reactions were noted after MSCs transplantation.

Corrected therapy prescribed: eplerenon – 25 mg; bisoprolol fumarate – 25 mg; empagliflozin – 10 mg; apixaban – 5 mg 2 times a day; amiodarone hydrochloride – 200 mg per day under heart rate control; torasemide – 10 mg per day; ademetionine 1,4-butandisulfonate – 500 mg 2 times a day.

On the 11th day after repeat hospitalization, the patient was discharged for further treatment and observation by a cardiologist at his place of residence with minimal positive dynamics: there were no more attacks of acute left ventricular failure, BP stabilized at 105–110/70 mm Hg, HR at 66 beats per minute, RR at 18 breaths per minute, and OS at 94% while breathing ambient air; peripheral oedema was absent. However, low tolerance to physical exertion persisted in the form of shortness of breath when walking up to 100–150 m, as well as general weakness and increased fatigue.

During the further observation period of 1 month, the patient noted moderate positive dynamics (improvement of the general condition and some increase in tolerance to physical exertion). In addition, the dose of diuretics was reduced, after which the patient did not experience peripheral oedema or signs of transudate accumulation in the abdominal and pleural cavities.

Control EchoCG (1 month after first cell infusion): dilatation of the left ventricle reduced, mitral valve regurgitation reduced, contractility of the left ventricle improved, hypokinesia on the back wall of the left ventricle and the interventricular septum remains; LV EF – 31%; LV EDS – 7.4 cm; LV ESS – 6.3 cm; LV EDV – 295 ml; LV ESV – 205 ml; LV SV – 90 ml; TIS – 0.91 cm; TPWL – 1.11 cm; I-II degree mitral valve insufficiency; RV SP – 28 mm Hg; LAS – 6.8[^]6.1 cm; LAV – 108 ml; no traces of effusion in both pleural cavities.

Daily ECG monitoring (Holter): ventricular extrasystoles, detected during the previous study, were not registered

Along with continued conservative therapy, a repeat intravenous infusion of 4,000,000 autologous MSCs was performed. No reactions were noted after MSCs transplantation.

During the next month, the patient noted a subsequent gradual increase in tolerance to physical exertion: by the end of this period, he no longer experienced general weakness, was able to climb to the 5th floor on his own, and returned to work (conducting military training). The severity of heart failure had improved to degree B.

Control EchoCG (1 month after second cell infusion): dilatation of the left ventricle and mitral valve regurgitation reduced further more, contractility of the left ventricle improved; LV EF – 35%; LV EDS – 6.9 cm; LV ESS – 5.6 cm; LV EDV – 246 ml; LV ESV – 158 ml; LV SV – 88 ml; TIS – 0.91 cm; TPWLV – 1.11 cm; I degree mitral valve insufficiency; RV SP – 26 mm Hg; LAS – $6.7^{*}5.6$ cm; LAV – 77 ml; no traces of effusion in both pleural cavities.

Clinical observation of the patient continues.

Discussion. Our case has demonstrated the prospects of the clinical use of autologous MSCs as a new palliative method of treatment for DCMP. It has been shown that double intravenous introduction of MSCs leads to a gradual improvement in general left ventricular contractility (LVEF increased from 25% at the start of cell therapy to 31% one month after the first cell introduction and 35% one month after the second cell introduction), a gradual reduction in both systolic and diastolic left ventricular volumes (from 227 ml and 305 ml to 205 ml and 295 ml one month after the first introduction, and to 158 ml and 246 ml one month after the second introduction), a reduction in left atrial volume (from 105 ml at the start to 77 ml only at the end of the monthly period after the second introduction), and, consequently, a regression in the severity of mitral regurgitation (from grade II at the start to grade I already after the first introduction, with no further progression), along with a slight decrease in pulmonary hypertension (from 30 mmHg at the start to 28 mmHg one month after the first introduction and 26 mmHg one month after the second introduction). It also contributed to the complete elimination of persistent ventricular extrasystole already after the first application.

These functional changes allowed for the alleviation of CHF manifestations, prevention of new episodes of acute left ventricular failure, reduction in the dose of diuretics, and an increase in the patient's tolerance to physical exertion. Similar effects of MSCs on damaged myocardium have been confirmed by other studies, which differ in methods of cell delivery and in the origin of cardiac dysfunction, but all indicate a dose-dependent increase in LVEF in patients with CHF. Accordingly, the use of MSCs can be considered one of the "bridges" to heart transplantation [12].

Nowadays, the expediency and effectiveness of different types of SCs in various heart muscle lesions is one of the main issues in all ongoing clinical studies. For example, along with MSCs, SCs from peripheral blood collected from related and unrelated donors are increasingly used [4]. There is an opinion, based on meta-analyses, that compared to bone marrow MSCs, the use of peripheral blood

SCs increases the incidence of "graft-versus-host disease" (GVHD) and worsens the overall prognosis [6]. To date, no randomized clinical trials have been completed comparing the use of peripheral blood SCs with other types. Autologous SCs have a number of advantages over cells from other sources due to their greatest potential for division and differentiation, as well as their proven safety in use [2].

Another important issue in SC application is the method of their delivery and mobilization to the affected area. The number of cells reaching the lesion, their survival during and after injection, and their effect on other tissues all depend on the method of administration. At present, there is no consensus on the optimal method of SC transplantation (TSC); each approach has its own advantages and limitations.

The infusion method of delivery, as demonstrated in our case, was one of the first methods of TSC. The advantage of this method is its ease of use and minimal invasiveness, allowing the procedure to be repeated multiple times with minimal risk [7]. Despite the positive experimental results obtained, the intravenous method has not become the primary approach, as the tropism of cells to other organs, such as the lungs and the reticuloendothelial system, reduces the number of SCs reaching the damaged myocardium, thereby limiting the clinical application of this method. Since the homing and retention of SCs are more pronounced in ischemic areas, this technique is considered more suitable in cases of acute myocardial infarction and has certain limitations when used in patients with CHF [11].

The second main direction includes numerous injection methods of SC delivery. They can be divided into intracoronary (intra-arterial, intravenous) and intramyocardial (direct, transventricular) techniques.

The selective intracoronary application, using standard balloon catheters and access through the femoral or radial artery, ensures the maximum concentration of SCs in a specific area of the myocardium. This method is mainly used in acute myocardial infarction or ischemic cardiomyopathy, as it can be performed simultaneously with percutaneous coronary intervention. Many studies demonstrate an improvement in myocardial perfusion and regional left ventricle wall contraction, an increase in LV EF, and a reduction of LV EDV [3]. However, despite its considerable advantages, this technique has certain limits in the clinic due to invasiveness, significant X-ray exposure for both the surgeon and the patient, occasion of significant stenoses in the coronary arteries, the risk of microthromboembolism [9].

In patients with significant stenoses of the coronary arteries, SCs can also be delivered intravenously with navigation guided by intravascular ultrasound (IVUS). The advantage of this method is its relative safety in contrast to the more common arterial application. The disadvantages of the method include difficulties in introducing SCs into

the area of the myocardium supplied by the right coronary artery, the variable anatomy of the heart veins, and the challenges of navigating the patient's venous system [5].

Direct intramyocardial SC administration can usually be performed during thoracotomy for open-heart surgery or as a stand-alone procedure that does not require cardiac arrest and is performed through a lateral mini-thoracotomy. This approach ensures precise and controlled introduction of the cellular drug into the specified area of the myocardium, avoiding such problems as mobilization and homing of transplanted SCs, as well as microembolization. It may be the preferred method of delivery in patients with chronic coronary artery occlusion. The disadvantages of this method include its invasiveness, significant risks of myocardial perforation at the injection site, and the occurrence of life-threatening arrhythmias. It should be noted that the direct injection of SCs into ischemic or sclerosed myocardium with limited blood supply may, in some cases, be accompanied by a deterioration in their survival in that area [10].

With the advent of NOGA navigation system (Biosense Webster, Diamond Bar, CA, USA), it became possible to use accurate intramyocardial injections through the catheter from the cavity of the heart chambers. NOGA captures changes in the magnetic field, providing a clear and high-quality visualization of myocardial ischemic zones, which makes it possible to obtain a 3D image in real time and distinguish the infarcted area from healthy and hibernated myocardium. Many clinical and experiment trials, concerning this method, demonstrate its safety and improvement in cardiac contractility in chronic left ventricular dysfunction [14]. At the same time, studies on NOGA machines are longer and require more highly qualified personnel. Also, it was shown in experiments that the implantation of MSCs in the myocardium via this method leads to a decrease in the speed of excitation, which increases the frequency of re-entry waves and ventricular rhythm disturbances [15].

Non-specific complications of TSCs appear quite rarely and are associated with violations of protocols and regulations of TSCs and accompanying medical manipulations [1].

Conclusions. The use of autologous MSCs partially restores the systolic function of the affected heart muscle, making it a promising palliative approach in the complex treatment of persistent CHF associated with DCMP. To date, a differentiated approach to selecting the optimal treatment strategy and delivery method for a particular type of SCs has not been developed. When determining the appropriate TSC technique, it is essential to carefully balance the expected benefits against the potential risks of various complications.

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Трансплантація аутологічних мезенхімальних стовбурових клітин в лікуванні хронічної серцевої недостатності при дилатаційній кардіоміопатії: клінічне спостереження

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Резюме

Вступ. Дилатаційна кардіоміопатія (ДКМП) складає значну частку серед некоронарогенних захворювань серця, які призводять до хронічної серцевої недостатності (ХСН). Через високу летальність, властиву ДКМП, відбувається постійний пошук альтернативних серцеберігаючих методів її лікування в якості «містків» до серцевої трансплантації. Серед них існує такий перспективний напрямок, як клітинна терапія.

Мета. На прикладі власного клінічного випадку показати ефективність паліативного лікування хронічної серцевої недостатності, спричиненої дилатаційною кардіоміопатією, методом внутрішньовенного введення аутологічних мезенхімальних стволових клітин.

Клінічний випадок. Чоловік, 48 років, хворий на ДКМП, проходив спеціалізоване лікування з приводу ХСН стадії С в кардіологічному відділенні Харківського обласного кардіологічного центру. Окрім медикаментозної терапії згідно із загальноновизнаними протоколами, двічі було застосоване внутрішньовенне введення аутологічних мезенхімальних стовбурових клітин (МСК) з інтервалом у 1 місяць між процедурами.

Перша ін'єкція, яка містила 6 млн МСК, виконувалася на тлі ознак гострої лівошлуночкової недостатності (ГЛШН), що приєдналася до вже наявної клінічної картини ХСН. На момент повторної ін'єкції, із застосуванням 4 млн МСК, явищ ГЛШН не спостерігалось.

Оцінку клінічного статусу пацієнта, а також основних функціональних параметрів його серця під час та через 1 місяць після кожної процедури проводили за допомогою фізикального обстеження, ехокардіографії та добового моніторингу електрокардіограми за Холтером.

Після обох ін'єкцій не відмічено ускладнень або побічних явищ.

Обговорення. За допомогою вищенаведених інструментальних методів дослідження було виявлено, що в результаті дворазового внутрішньовенного введення аутологічних МСК спостерігалось поступове покращення загальної скоротливості лівого шлуночка, поступове скорочення систолічного та діастолічного об'ємів лівого шлуночка, зменшення об'єму лівого передсердя, зниження важкості мітральної регургітації з II до I ступеня, а також купірування персистуючої шлуночкової екстрасистолії. Одночасно з цими функціональними змінами відмічено послаблення клінічних проявів ХСН зі стадії С до стадії В, відсутність нових епізодів ГЛШН, можливість

зменшення дози діуретичних препаратів без затримки рідини в організмі, а також покращення витривалості пацієнта щодо фізичних навантажень.

Позитивна динаміка в клінічному стані хворого, а також у його ехокардіографічних показниках, відзначалася вже через 1 місяць після кожного введення клітин.

Висновки. Внутрішньовенне введення аутологічних МСК частково відновлює систолічну функцію ураженого міокарда у хворих на ДКМП з клінікою персистоючої ХСН, отже, може розглядатися як перспективний паліативний напрям у комплексному лікуванні цієї категорії хворих. Методологія його застосування, ізольовано або в поєднанні з іншими методами, потребує подальшого уточнення. Через відносно невеликий світовий клінічний досвід наразі ще не розроблено диференційованого підходу до вибору оптимального способу введення певного типу стовбурових клітин залежно від характеру ураження міокарда.

Ключові слова: клітинна терапія, систолічна дисфункція, альтернативне серцевозберігаюче лікування, «міст» до серцевої трансплантації, паліативне лікування.

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