Original article

Kardiologia Polska
2011; 69, 12: 1234–1240
ISSN 0022–9032

The effects of intracoronary delivery of mononuclear bone marrow cells in patients with myocardial infarction: a two year follow-up results

Michał Plewka[1], Maria Krzemińska-Pakuła[1], Jan Z. Peruga[1], Piotr Lipiec[2], Małgorzata Kurpesa[1], Karina Wierzbowska-Drabik[1], Anna Korycka-Wołowiec[3], Jarosław D. Kasprzak[1]

[1]Department of Cardiology, Chair of Cardiology, Medical University of Lodz, Lodz, Poland
[2]Department of Rapid Cardiac Diagnostics, Chair of Cardiology, Medical University of Lodz, Lodz, Poland
[3]Department of Haematology, Medical University of Lodz, Lodz, Poland

Abstract

Background: Transplantation of bone marrow stem cells (BMSC) is a new method of prevention of left ventricular (LV) remodelling in post-infarction patients. Studies published to date point to LV systolic and diastolic function improvement following this therapy however only a few studies assessed the long-term effects of BMSC.

Aim: To assess the 2 year prognosis in patients with anterior myocardial infarction (MI) treated with BMSC transplantation in the acute phase.

Methods: The study group consisted of 60 patients with first anterior ST-segment elevation MI (STEMI), treated with primary percutaneous angioplasty, with baseline LV ejection fraction (LVEF) < 40%, who were randomly assigned to undergo BMSC transplantation on day 7 of the STEMI (40 patients, BMSC group) or to receive standard treatment (20 patients, control group). In all the patients echocardiography was performed at baseline and after 1, 3, 6, 12 and 24 months. The composite end-point (death, MI, admission for heart failure or repeat revascularisation) was assessed after 2 years of follow-up.

Results: Absolute increase of LVEF compared to baseline values was higher in the BMSC group than in the control group. The LVEF increase in BMSC group at 1 month was 7.1% (95% CI 3.1–11.1%), at 6 months — 9.3% (95% CI 5.3–13.3%), at 12 months — 11.0% (95% CI 6.2–13.3%) and at 24 months — 10% (95% CI 7.2–12.1%). In the control group, LVEF increase was 3.7% (95% CI 2.3–9.7%) at 1 month, 4.7% (95% CI 1.2–10.6%) at 6 months, 4.8% (95% CI 1.5–11.0%) at 12 months and 4.7% (95% CI 1.4–10.7%) at 24 months. The composite end-point occurred significantly more frequently in the control group (55%) than in the BMSC group (23%): OR 2.72; 95% CI 1.06–7.02, p = 0.015.

Conclusions: Treatment with mononuclear bone marrow cells on day 7 of the first anterior MI in patients with significant baseline systolic dysfunction improves 2-year outcome.

Key words: mononuclear bone marrow cells, stem cells, ST-segment elevation myocardial infarction, left ventricular function, prognosis

Kardiol Pol 2011; 69, 12: 1234–1240

INTRODUCTION

The progress in interventional cardiology that has taken place in the recent years and the growing use of primary percutaneous revascularisation in patients with myocardial infarction (MI) have resulted in better prognosis in a substantial proportion of this patient population. However, in some patients effective revascularisation cannot be performed or is performed too late, when a significant number of contractile units is lost [1].

Address for correspondence:
Michał Plewka, MD, PhD, Department of Cardiology, Chair of Cardiology, Medical University of Lodz, ul. Kniaziewicza 1/5, 91–347 Łódź, Poland, tel/fax: +48 42 653 99 09, e-mail: plewka@ptkardio.pl
Received: 23.03.2011 **Accepted:** 08.06.2011

This prompts the constant search for new methods of post-infarction injury prevention, especially in patients with extensive anterior MI. One of the promising modern methods of adjuvant treatment after revascularisation procedures is the transplantation of stem cells which are capable of differentiation into various cell lines. It should be underlined, that the leading international studies in the field were conducted also in Poland [2–4].

In the recent years major interest was focused on mononuclear bone marrow cells, a heterogenous cell population, including a fraction of bone marrow stem cells (BMSC), with positive CD34 and CD133 surface antigens [5]. The mechanisms of potential beneficial effects of BMSC on myocardial function after MI are not completely understood. According to the classical theory after getting to the site of myocardial injury, are capable of differentiation into mature cardiomyocytes and direct regeneration of the injured myocardial tissue [6]. The results of labelled CD 133+ cell colonies demonstrated however, that the number of stem cells remaining in the target post-infarction injury zone is rather small.

With use of the SPECT technique it has been demonstrated that < 10% of the radiolabelled stem cells remained within the myocardium, whereas the majority migrated to the liver and to the spleen [7]. In another investigation, only 3% of the cells remained in the scarred area after intracoronary injection [8]. Most recent studies demonstrated that the fundamental clinical significance can be due to indirect mechanisms of BMSC effect [9].

It is believed that stem cells, through their paracrine activity, can promote neovascularisation, modify cytokine production, be incorporated in the host cells and mobilise stem cells in the bone marrow by producing favourable chemokine gradients [10, 11]. Many studies have demonstrated that BMSC transplantation is feasible and safe, and can be an effective adjuvant therapy to conventional revascularisation [12––15]. Metaanalyses [16–18] have shown moderate increase of systolic function. In a small number of studies, BMSC effects on diastolic function were investigated [19, 20]. In the literature to date, there are only a few studies assessing long-term prognosis in MI patients treated with BMSC [21].

The aim of the study was to assess the 2 year outcome of patients with anterior MI treated with BMSC transplantation in the acute phase.

METHODS

Study group

The study group consisted of 60 patients, who were included in a randomised study assessing multidirectional effects of BMSC transplantation between 2005–2007, as a part of the Polish Ministry of Science and Higher Education research project No. 2P05B 178 28 [22]. Consecutive patients with first ST-elevation anterior MI and baseline left ventricular ejection fraction (LVEF) < 40% were included in the study. The STEMI diagnosis criteria were as follows: symptoms of ischaemia, ST-segment elevation in ECG and significant troponin elevation, with at least one measurement exceeding 99 percentile of the reference range. Within 12 h of the symptom onset, all patients were successfully treated with percutaneous coronary intervention (PCI) of the left anterior descending coronary artery (LAD) with bare metal stent implantation and TIMI 3 flow post intervention.

Exclusion criteria were as follows: history of MI, multivessel coronary disease, current infection, confirmed cancer diagnosis or other disorders that could potentially effects prognosis or patient compliance. Patients were randomly assigned to BMSC transplantation or to the control group in 2:1 proportion (40 and 20 patients, respectively). In the control group, due to ethical reasons, bone marrow harvesting and intracoronary delivery of BMSC were not performed.

Pharmacological treatment was in accordance with the current guidelines for the management of STEMI, Inclusion in the study and randomisation had no impact on further in-hospital and long-term pharmacological management. The study was approved by the Ethical Committee of the Medical University of Lodz. All patients expressed their informed consent to the participation in the study.

Harvesting and delivery of mononuclear bone marrow cells

The procedure of harvesting and delivery of mononuclear bone marrow cells was performed at days 3–11 (mean: day 7) of STEMI. The harvesting of mononuclear bone marrow cells, as well as the assessment of CD34 and CD133 antigen expression with flow cytometry was done in all patients in the Department of Haematology, Medical University of Lodz. The detailed methodology was described in an earlier publication [23].

The aspiration of bone marrow was performed in the operating room under local anaesthetic (2% lidocaine solution) and intravenous sedation with midanium 0.1 mg/kg and fentanyl 25–50 mg IV. By puncture of both iliac crests 100 mL of bone marrow was aspirated. Isolation procedure of the mononuclear bone marrow cells was carried out in aseptic conditions in the specially designed for that purpose and fulfilling safety criteria laminar safety cabinet Safe Flow 1.2 (Bioair, USA).

Within 2 h of its preparation, the mononuclear bone marrow cell suspension was delivered via intracoronary route in the Catheterisation Laboratory of the Cardiology Department, Medical University of Lodz. The procedure was done via right radial artery. With use of an over the wire balloon catheter (Ninja, Cordis), distally to the site of occlusion of the LAD that had been recanalised during the acute phase of STEMI, 20 mL of the suspension was administered in 4 portions of 5 mL over 2-min period, with 2-min break between consecutive balloon inflations. The average number of the mononuclear bone marrow cells was $1.44 \pm 0.49 \times 10^8$ (range 0.3 to 3.0×10^8).

Echocardiographic and clinical assessment

In our study the primary composite end point (death, MI, repeat revascularisation, readmission for heart failure (HF) progression) was assessed at discharge and at 1, 3, 6, 12 and 24 months after the index MI.

In all the patients echocardiography was performed with VIVID 7 Dimension (GE Vingmed Ultrasound AS, Horten, Norway), in standard parasternal and apical views. Left ventricular end-systolic (LVESV) and end-diastolic (LVEDV) volumes as well as LVEF by biplane Simpson method were calculated. Repeat echocardiography was performed after 1, 3, 6, 12 and 24 months. In the previously reported studies, detailed results were published concerning broadened echocardiographic assessment including speckle tracking [24, 25], Holter monitoring [26], as well as radionuclide [27] and angiographic [28] assessment.

Statistical analysis

Numerical variables are presented as mean values ± SD. Student *t*-test was used for between-group comparisons of variables following normal distribution, and U Mann-Whitney test for other variables. Survival curves were plotted according to the Kaplan-Meier method. Small number of patients in the study group precluded analysis of the separate elements of the composite end-point. Hence, the analysis was confined to the composite end-point. The statistical analysis was performed with the use of MedCalc software (Frank Schoonjans, version 9.6.4.0, 2008). A p value < 0.05 was considered statistically significant.

Table 1. Baseline characteristics of the study groups

Parameter	BMSC groups (n = 40)	Control group (n = 20)	P
Age [years]	56 ± 9	56 ± 9	NS
Women	13 (33%)	5 (25%)	NS
Body mass [kg]	77.6 ± 13.2	79.9 ± 11.8	NS
Hypertension	17 (42%)	8 (40%)	NS
Hypercholesterolaemia	17 (42%)	7 (35%)	NS
Diabetes	4 (10%)	2 (10%)	NS
Smoking	22 (55%)	10 (50%)	NS
LVEDV [mL]	149 ± 48	151 ± 65	NS
LVESV [mL]	95 ± 39	99 ± 49	NS
LVEF [%]	35 ± 6	33 ± 7	NS

LVEF — left ventricular ejection fraction; LVEDV — left ventricular end-diastolic volume; LVESD — left ventricular end-systolic volume

Table 2. Cardiac events during 2-year follow-up

End-point	BMSC	Controls
Death	2 (5%)	2 (10%)
Myocardial infarction	1 (3%)	1 (5%)
Revascularisation	5 (13%)	3 (15%)
Admission for heart failure	1 (3%)	5 (15%)
Composite end-point	9 (23%)	11 (55%)

RESULTS

Baseline clinical characteristics and basic echocardiographic parameters are presented in Table 1. Chamber dimensions, LVESV and LVEDV at baseline were similar in both groups and reflected the significant LV systolic dysfunction. The LVEF also did not differ significantly between the groups.

Pharmacological treatment in the BMSC and control groups was similar. Beta-adrenergic receptor blockers were used by 92% and 90% of patients, respectively. Angiotensin converting enzyme inhibitors — 92% and 85% patients, respectively, whereas statins, clopidogrel (up to 12 months) and aspirin were prescribed to all patients.

On standard echocardiography at follow-up after 1, 6, 12 and 24 months LVEF improvement was demonstrated in the BMSC as well as in the control group. Net LVEF gain relative to baseline values was higher in BMSC than in the control group. The LVEF increase at 1 month in BMSC group was 7.1% (95% CI 3.1–11.1%), at 6 months — 9.3% (95% CI 5.3–13.3%), at 12 months — 11.0% (95% CI 6.2–13.3%) and at 24 months — 10% (95% CI 7.2–12.1%). On the other hand, LVEF increase in the control group was 3.7% (95% CI 2.3–9.7%) at 1 month, 4.7% (95% CI 1.2–10.6%) at 6 months, 4.8% (95% CI 1.5–11.0%) at 6 months, and 4.7% (95% CI 1.4–10.7%) at 24 months.

During 24 months of follow-up 2 patients from BMSC group died (one sudden cardiac death within the first month, 1 death due to repeat infarction at 3 months). In the control group, two sudden cardiac deaths occurred within the first months. In Table 2, the remaining cardiac events recorded at follow-up are presented. Patients from the control group more frequently required repeat hospitalisation for HF than patients after BMSC transplantation. The majority of admissions occurred late (6–24 months). The composite end-point was significantly more frequent in the control group than in the BMSC group (odds ratio 2.72; 95% CI 1.06–7.02, p = 0.015). The event-free Kaplan Meier survival plots in both groups are presented in Figure 1.

DISCUSSION

In the present study we demonstrated a significant reduction in the composite — end-point in patients treated with BMSC transplantation compared with the control group after 24-months of follow-up.

A small sample size precluded the statistical analysis of mortality difference, although mortality rate in the BMSC group was halved in comparison with the control group (5% *vs* 10%). The composite end-point difference was primarily driven by decreased hospitalisations for HF, predominantly between

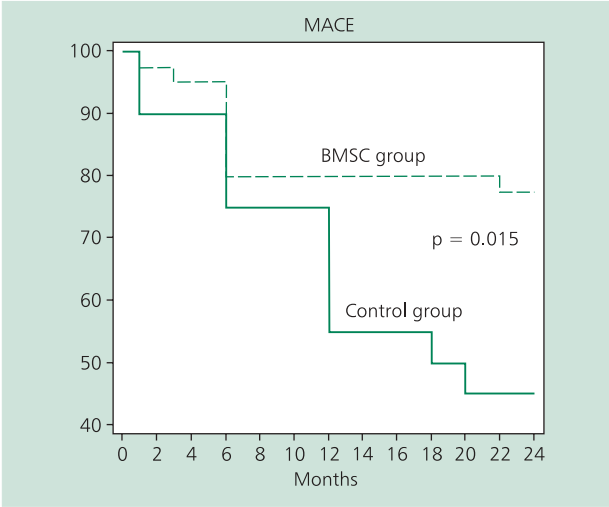

Figure 1. Event-free Kaplan-Meier survival curves (composite end-point — MACE) in 2 year follow-up

12 and 24 months. This corresponds well with the improvement of LV systolic function, as the difference between BMSC and control groups persisted through 12 to 24 months. Better outcome after transplantation could also be related to better diastolic function in this patient group, which was described earlier [19].

The increase of LVEF and long-term clinical effects in our study were more pronounced than in the previously published meta-analysis of Lipinski et al. [17], where LVEF change was 3%. The difference can be due to greater systolic dysfunction at baseline in our study, as the meta-analysis included studies in which baseline LV function was relatively preserved. In the REPAIR-AMI [29] and REGENT [30] studies greater benefit was demonstrated in patients with significantly impaired LVEF.

In a metaanalysis by Martin-Rendon et al. [18] potential causes of discrepant clinical effects of BMSC transplantation were investigated. It was found that the effects of BMSC administration at 4–7 days post MI were better than if such treatment was implemented at earlier stages — i.e. within 24 h. Significant improvement of LV function (LVEF increase of 4.6%, $p = 0.01$) was associated with the composite end-point reduction (death, MI, infarct-related artery restenosis, life-threatening ventricular arrhythmia) in comparison to the control group. In the studies in which BMSC were administered within 24 h, significant benefits were not observed. The authors explained these results of plasma cytokines such as VEGF, HGF, or G-CSF during the first week after MI. In our study, stem cells were administered at day 7 on average, between day 6 and day 8 in 60% of patients, which represents optimal time point for the procedure according to recently published data.

It was also found that the number of stem cells that allows for LV function improvement equals 10^8. The number of mononuclear bone marrow cells administered in our study was greater ($1.44 \pm 0.49 \times 10^8$) than in the ASTAMI study subanalysis [31], in which no significant improvement of the LV function was noted in comparison to the control group. It should be also mentioned that in the REGENT study [30], no advantage of intracoronary delivery of isolated $CD34^+CXCR4^+$ cells was demonstrated in comparison to non-selected suspension of mononuclear bone marrow cells.

In one of the earlier studies of stem cell transplantation in MI patients, the REPAIR-AMI [21] study, the effects of the therapy on 2-year prognosis was investigated. The composite end-point (death, MI, need for revascularisation) occurred significantly less frequently in the BMSC-treated group (hazard ratio 0.58, 95% CI 0.36–0.94, $p = 0.025$). Similar to our study, a reduction of the composite end-point related to progression of HF (death, admission for HF progression) was noted (hazard ratio 0.26; 95% CI 0.085–0.77, $p = 0.015$). In multivariable analysis BMSC treatment was independently related to improved prognosis.

The results of the longest, 5-year follow-up of 62 patients after BMSC therapy were published by the BALANCE study investigators [32]. Echocardiography performed at 3 months showed a significant improvement of LVEF and cardiac output. The infarct area decreased by 8%. On subsequent examinations, 12 and 60 months after treatment, these benefits were sustained, compared to the control group. Moreover, exercise capacity was improved and, most importantly, mortality reduction was demonstrated in comparison with the control group.

In a study by Grajek et al. [33] despite the lack of significant difference between BMSC and control groups with regard to LVEF, there was improvement of myocardial perfusion on Tc-99 MIBI SPECT with dipiridamole and better prognosis in the BMSC treated group ($p = 0.0027$). The authors suggested that this can be related to favourable effects of BMSC on coronary microcirculation.

In the FINCELL [34] study however, no differences in cardiac event rates were found between the BMSC and control groups at 6 months. It should be kept in mind, that in that study patients with preserved baseline LVEF were included (mean LVEF 59% ± 11% in BMSC group). Similarly, in a multicentre study HEBE [35], no clinical benefits were demonstrated in patients with first MI treated with mononuclear cells harvested from bone marrow or from circulating blood.

Currently, several new multi-centre studies are being carried out, such as SWISS-AMI [36], COMPARE-AMI [37] or MYSTAR [38]. Their results will allow for assessment of cell therapy effectiveness in MI patients.

Limitations of the study

The major limitation of our study is the small sample size. Additionally, no bone marrow harvesting or intracoronary delivery of placebo were performed in the control group.

CONCLUSIONS

Treatment with mononuclear bone marrow cell transplantation on day 7 of the first anterior MI in patients with significant baseline systolic dysfunction, improves prognosis at 2 years.

The work was partially funded by Polish Ministry of Science Grant No. 2PO5B 178 28.

Conflict of interest: *none declared*

References

1. Lloyd-Jones D, Adams R, Carnethon M et al.; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics — 2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation, 2009; 119: 480–486.
2. Siminiak T, Kalawski R, Krupisz M. Myoblast transplantation in the treatment of postinfarction myocardial contractility impairment: a case report. Kardiol Pol, 2002; 56: 131–133.
3. Siminiak T, Grygielska B, Jerzykowska O et al. Autologous bone marrow stem cell transplantation in acute myocardial infarction — report of two cases. Kardiol Pol, 2003; 59: 502–510.
4. Siminiak T, Fiszer D, Jerzykowska O, Grygielska B, Kałmucki P, Kurpisz M. Percutaneous autologous myoblast transplantation in the treatment of post-infarction myocardial contractility impairment: report on two cases. Kardiol Pol, 2003; 59: 492–501.
5. Forrester JS, White AJ, Matsushita S, Chakravarty T, Makkar RR. New paradigms of myocardial regeneration post-infarction: tissue preservation, cell environment, and pluripotent cell sources. J Am Coll Cardiol Cardiovasc Interv, 2009; 2: 1–8.
6. Li TS, Hayashi M, Ito H et al. Regeneration of infarcted myocardium by intramyocardial implantation of ex vivo transforming growth factor-beta-preprogrammed bone marrow stem cells. Circulation, 2005; 111: 2438–2445.
7. Kurpisz M, Czepczyński R, Grygielska B et al. Bone marrow stem cell imaging after intracoronary administration. Int J Cardiol, 2007; 121: 194–195.
8. Hofmann M, Wollert KC, Meyer GP et al. Monitoring of bone marrow cell homing into the infarcted human myocardium. Circulation, 2005; 111: 2198–2202.
9. Perez-Ilzarbe M, Agbulut O, Pelacho B et al. Characterization of the paracrine effects of human skeletal myoblasts transplanted in infarcted myocardium. Eur J Heart Fail, 2008; 10: 1065–1072.
10. Lee BC, Hsu HC, Tseng WY et al. Cell therapy generates a favourable chemokine gradient for stem cell recruitment into the infarcted heart in rabbits. Eur J Heart Fail, 2009; 11: 238–245.
11. Wojakowski W, Tendera M, Michałowska A et al. Mobilization of CD34/CXCR4+, CD34/CD117+, c-met+ stem cells, and mononuclear cells expressing early cardiac, muscle, and endothelial markers into peripheral blood in patients with acute myocardial infarction. Circulation, 2004; 110: 3213–3220.
12. Strauer BE, Brehm M, Zeus T et al. Repair of infarcted myocardium by autologous intracoronary mononuclear bone marrow cell transplantation in humans. Circulation, 2002; 106: 1913–1918.
13. Wollert KC, Meyer GP, Lotz J et al. Intracoronary autologous bone-marrow cell transfer after myocardial infarction: the BOOST randomised controlled clinical trial. Lancet, 2004; 364: 141–148.
14. Ge J, Li Y, Qian J et al. Efficacy of emergent transcatheter transplantation of stem cells for treatment of acute myocardial infarction (TCT-STAMI). Heart, 2006; 92: 1764–1767.
15. Schächinger V, Assmus B, Britten MB et al. Transplantation of progenitor cells and regeneration enhancement in acute myocardial infarction: final one-year results of the TOPCARE-AMI Trial. J Am Coll Cardiol, 2004; 44: 1690–1699.
16. Abdel-Latif A, Bolli R, Tleyjeh IM et al. Adult bone marrow-derived cells for cardiac repair: a systematic review and meta-analysis. Arch Intern Med, 2007; 167: 989–997.
17. Lipinski MJ, Biondi-Zoccai GG, Abbate A et al. Impact of intracoronary cell therapy on left ventricular function in the setting of acute myocardial infarction: a collaborative systematic review and meta-analysis of controlled clinical trials. J Am Coll Cardiol, 2007; 50: 1761–1767.
18. Martin-Rendon E, Brunskill SJ, Hyde CJ, Stanworth SJ, Mathur A, Watt SM. Autologous bone marrow stem cells to treat acute myocardial infarction: a systematic review. Eur Heart J, 2008; 29: 1807–1818.
19. Plewka M, Krzemińska-Pakuła M, Lipiec P et al. Impact of intracoronary transplantation of mononuclear bone marrow stem cells on diastolic function in patients with acute myocardial infarction. Pol Przegl Kardiol, 2009; 11: 249–254.
20. Schaefer A, Meyer GP, Fuchs M et al. Impact of intracoronary bone marrow cell transfer on diastolic function in patients after acute myocardial infarction: results from the BOOST trial. Eur Heart J, 2006; 27: 929–935.
21. Assmus B, Rolf A, Erbs S et al.; REPAIR-AMI Investigators. Clinical outcome 2 years after intracoronary administration of bone marrow-derived progenitor cells in acute myocardial infarction. Circ Heart Fail, 2010; 3: 89–96.
22. Plewka M. Ocena efektów dowieńcowej transplantacji komórek macierzystych szpiku kostnego u pacjentów z zawałem mięśnia sercowego z uwzględnieniem echokardiograficznej metody śledzenia markerów akustycznych. Rozprawa habilitacyjna, Uniwersytet Medyczny w Łodzi, Łódź 2010.
23. Korycka A, Plewka M, Krawczynska A et al. The evaluation of efficacy of bone marrow CD34+ and CD133+ cells isolated from patients with acute myocardial infarction. Acta Haematologica Polonica, 2008; 39: 73–86.
24. Plewka M, Krzemińska-Pakuła M, Jeżewski T et al. Early echocardiographic assessment of coronary flow reserve after intracoronary administration of bone marrow stem cells in patients with myocardial infarction. Pol Przegl Kardiol, 2008; 10: 48–53.
25. Plewka M, Krzemińska-Pakuła M, Lipiec P et al. Effect of intracoronary injection of mononuclear bone marrow stem cells on left ventricular function in patients with acute myocardial infarction. Am J Cardiol, 2009; 104: 1336–1342.
26. Trzos E, Krzemińska-Pakuła M, Rechciński T et al. The effects of intracoronary autologous mononuclear bone marrow cell transplantation on cardiac arrhythmia and heart rate variability. Kardiol Pol, 2009; 67: 713–721.
27. Lipiec P, Krzemińska-Pakuła M, Plewka M et al. Impact of intracoronary injection of mononuclear bone marrow cells in acute myocardial infarction on left ventricular perfusion and function: a 6-month follow-up gated 99mTc-MIBI single-photon emission computed tomography study. Eur J Nucl Med Mol Imag, 2009; 36: 587–593.
28. Peruga J, Plewka M, Kasprzak J et al. Intracoronary administration of stem cells in patients with acute myocardial infarction — angiographic follow-up. Kardiol Pol, 2009; 67: 485–486.
29. Dill T, Schächinger V, Rolf A et al. Intracoronary administration of bone marrow-derived progenitor cells improves left ventricular function in patients at risk for adverse remodeling after acute ST-segment elevation myocardial infarction: results of the Reinfusion of Enriched Progenitor cells And Infarct Remodeling in Acute Myocardial Infarction study (REPAIR-AMI) cardiac magnetic resonance imaging substudy. Am Heart J. 2009; 157: 541–547.
30. Tendera M, Wojakowski W, Ruzyłło W et al.; REGENT Investigators. Intracoronary infusion of bone marrow-derived selected CD34+CXCR4+ cells and non-selected mononuclear cells in patients with acute STEMI and reduced left ventricular ejection fraction: results of randomized, multicentre Myocardial Regeneration by Intracoronary Infusion of Selected Population of Stem

Cells in Acute Myocardial Infarction (REGENT) Trial. Eur Heart J, 2009; 30: 1313–1321.
31. Beitnes JO, Gjesdal O, Lunde K et al. Left ventricular systolic and diastolic function improve after acute myocardial infarction treated with acute percutaneous coronary intervention, but are not influenced by intracoronary injection of autologous mononuclear bone marrow cells: a 3 year serial echocardiographic sub-study of the randomized-controlled ASTAMI study. Eur J Echocardiogr, 201; 12: 98–106.
32. Yousef M, Schannwell CM, Köstering M, Zeus T, Brehm M, Strauer BE. The BALANCE Study: clinical benefit and long-term outcome after intracoronary autologous bone marrow cell transplantation in patients with acute myocardial infarction. J Am Coll Cardiol, 2009; 53: 2262–2269.
33. Grajek S, Popiel M, Gil L et al. Influence of bone marrow stem cells on left ventricle perfusion and ejection fraction in patients with acute myocardial infarction of anterior wall: randomized clinical trial: Impact of bone marrow stem cell intracoronary infusion on improvement of microcirculation. Eur Heart J, 2010; 31: 691–702.
34. Huikuri HV, Kervinen K, Niemelä M et al.; FINCELL Investigators. Effects of intracoronary injection of mononuclear bone marrow cells on left ventricular function, arrhythmia risk profile, and restenosis after thrombolytic therapy of acute myocardial infarction. Eur Heart J, 2008; 29: 2723–2732.
35. Hirsch A, Nijveldt R, van der Vleuten PA et al.; on behalf of the HEBE investigators. Intracoronary infusion of mononuclear cells from bone marrow or peripheral blood compared with standard therapy in patients after acute myocardial infarction treated by primary percutaneous coronary intervention: results of the randomized controlled HEBE trial. Eur Heart J, 2011; 32: 1736–1747.
36. Sürder D, Schwitter J, Moccetti T et al. Cell-based therapy for myocardial repair in patients with acute myocardial infarction: rationale and study design of the SWiss multicenter Intracoronary Stem cells Study in Acute Myocardial Infarction (SWISS-AMI). Am Heart J, 2010; 160: 58–64.
37. Mansour S, Roy DC, Bouchard V et al. COMPARE-AMI trial: comparison of intracoronary injection of CD133+ bone marrow stem cells to placebo in patients after acute myocardial infarction and left ventricular dysfunction: study rationale and design. J Cardiovasc Transl Res, 2010; 3: 153–159.
38. Nyolczas N, Gyöngyösi M, Beran G et al. Design and rationale for the Myocardial Stem Cell Administration After Acute Myocardial Infarction (MYSTAR) Study: a multicenter, prospective, randomized, single-blind trial comparing early and late intracoronary or combined (percutaneous intramyocardial and intracoronary) administration of nonselected autologous bone marrow cells to patients after acute myocardial infarction. Am Heart J, 2007; 153: 212.e1–e7.

Wpływ dowieńcowego podania komórek jednojądrzastych szpiku kostnego u chorych z zawałem serca na rokowanie w 2-letniej obserwacji

Michał Plewka[1], Maria Krzemińska-Pakuła[1], Jan Z. Peruga[1], Piotr Lipiec[2], Małgorzata Kurpesa[1], Karina Wierzbowska-Drabik[1], Anna Korycka-Wołowiec[3], Jarosław D. Kasprzak[1]

[1]Klinika Kardiologii, Katedra Kardiologii, Uniwersytet Medyczny w Łodzi, Łódź
[2]Zakład Szybkiej Diagnostyki Kardiologicznej, Katedra Kardiologii, Uniwersytet Medyczny w Łodzi, Łódź
[3]Klinika Hematologii, Uniwersytet Medyczny w Łodzi, Łódź

Streszczenie

Wstęp: Przeszczep komórek macierzystych szpiku kostnego (BMSC) jest nową metodą zapobiegania pozawałowej przebudowie lewej komory (LV) u pacjentów po zawale serca (MI). Dotychczas opublikowane prace wskazują na poprawę funkcji skurczowej i rozkurczowej LV, w pojedynczych badaniach oceniano wpływ BMSC na rokowanie w obserwacji odległej.

Cel: Celem pracy była ocena rokowania w 2-letniej obserwacji u pacjentów z MI poddanych transplantacji BMSC w ostrej fazie MI ściany przedniej.

Metody: Grupę badaną stanowiło 60 chorych z pierwszym MI ściany przedniej z uniesieniem odcinka ST (STEMI), leczonych pierwotną przezskórną angioplastyką, z wyjściową frakcją wyrzutową lewej komory (LVEF) < 40%, zrandomizowanych do transplantacji BMSC w 7. dobie STEMI (40 chorych, grupa BMSC) lub leczenia standardowego (20 chorych, grupa kontrolna). U wszystkich wykonywano badanie echokardiograficzne wyjściowe i kontrolne po 1, 3, 6, 12 i 24 miesiącach oraz oceniano wystąpienie złożonego punktu końcowego (zgon, MI, hospitalizacja z powodu niewydolności serca, ponowna rewaskularyzacja wieńcowa) w obserwacji 2-letniej.

Wyniki: Bezwzględny wzrost LVEF w odniesieniu do badania wyjściowego był większy w grupie BMSC niż w grupie kontrolnej. W grupie badanej po miesiącu wzrost LVEF wynosił 7,1% (95% CI 3,1–11,1%), po 6 miesiącach 9,3% (95% CI 5,3–13,3%), po 12 miesiącach 11,0% (95% CI 6,2–13,3%), a po 24 miesiącach 10% (95% CI 7,2–12,1%). W grupie kontrolnej wzrost LVEF wynosił odpowiednio: po miesiącu 3,7% (95% CI 2,3–9,7%), po 6 miesiącach 4,7% (95% CI 1,2–10,6%), po 12 miesiącach 4,8% (95% CI 1,5–11,0%), a po 24 miesiącach 4,7% (95% CI 1,4–10,7%). Złożony punkt końcowy wystąpił istotnie częściej w grupie kontrolnej (55%) niż leczonej za pomocą transplantacji BMSC (23%): OR 2,72; 95% CI 1,06–7,02; p = 0,015.

Wnioski: Leczenie za pomocą transplantacji komórek jednojądrzastych szpiku kostnego w 7. dobie u chorych z pierwszym MI ściany przedniej, z istotną wyjściową dysfunkcją skurczową LV, poprawia rokowanie w obserwacji 2-letniej.

Słowa kluczowe: komórki jednojądrzaste szpiku kostnego, komórki macierzyste, zawał serca z uniesieniem odcinka ST, funkcja lewej komory, prognoza

Kardiol Pol 2011; 69, 12: 1234–1240

Adres do korespondencji:
dr hab. n. med. Michał Plewka, Klinika Kardiologii, Katedra Kardiologii, Uniwersytet Medyczny w Łodzi, Szpital im. Wł. Biegańskiego, ul. Kniaziewicza 1/5, 91–347 Łódź, tel/faks: +48 42 653 99 09, e-mail: plewka@ptkardio.pl
Praca wpłynęła: 23.03.2011 r. **Zaakceptowana do druku:** 08.06.2011 r.