Journal of the American College of Cardiology Vol. 53, No. 24, 2009

ISSN 0735-1097/09/$36.00
doi:10.1016/j.jacc.2009.02.051

The BALANCE Study

Clinical Benefit and Long-Term Outcome After Intracoronary Autologous Bone Marrow Cell Transplantation in Patients With Acute Myocardial Infarction

Muhammad Yousef, MD, Christiana Mira Schannwell, MD, Mathias Köstering, MD, Tobias Zeus, MD, Michael Brehm, MD, Bodo Eckehard Strauer, MD

Düsseldorf, Germany

Objectives The aim of this study was to investigate the quantitative amount of improvement of ventricular hemodynamic status, geometry, and contractility as well as the long-term clinical outcome of cell-treated patients after acute myocardial infarction (AMI).

Background Animal experiments as well as clinical studies have demonstrated that autologous bone marrow cell (BMC) transplantation might improve ventricular function and prevent remodeling.

Methods Sixty-two patients underwent intracoronary autologous BMC transplantation 7 ± 2 days after AMI. Cells were infused directly into the infarct-related artery. The control group consisted of 62 patients with comparable left ventricular (LV) ejection fraction (EF) and diagnosis. All patients had several examinations (e.g., coronary angiography, right heart catheterization, biplane left ventriculography, electrocardiogram [ECG] at rest and exercise, echocardiography, late potential [LP], heart rate variability [HRV], and 24-h Holter ECG). The therapeutic follow-up was performed 3, 12, and 60 months after BMC therapy.

Results Three months after BMC therapy there was significant improvement of EF and stroke volume index. The infarct size was significantly reduced by 8%. Contraction velocities (lengths/second, volumes/second) increased significantly and the slope of the ventricular function curve (systolic pressure/end-systolic volume) became steeper. There was significant improvement of contractility in the infarct zone, as evidenced by a 31% increase of LV velocity of shortening (VCF), preferably in the border zone of the infarct zone. In contrast, the noninfarcted area showed no difference in VCF before and after BMC therapy. Furthermore, decreases of abnormal HRV, LP, and ectopic beats were documented after BMC therapy. Twelve and 60 months after BMC therapy the parameters of contractility, hemodynamic status, and geometry of the LV were stable. The exercise capacity of treated patients was significantly augmented, and the mortality was significantly reduced in comparison with the control group.

Conclusions BMC therapy leads to significant and longstanding improvements of LV performance as well as quality of life and mortality of patients after AMI. After BMC therapy, no side effects were observed, showing that BMC therapy is safe. (J Am Coll Cardiol 2009;53:2262–9) © 2009 by the American College of Cardiology Foundation

After acute myocardial infarction (AMI), a variety of structural and histopathological changes occur in the left ventricular (LV) myocardium (remodeling) that lead to progressive decline in LV performance. The infarcted area is unable to resist the pressure and volume load on the heart in the same manner as the healthy tissue. Consequently, there is dilatation of the chamber arising from the infarct region. Ventricular mass and volume increase, which together adversely affect cardiac function.

Medical treatment or revascularization after AMI can improve the function of viable or hibernating myocardium, but cannot restore necrotic myocardial tissue. Current therapy strategies are limited in the prevention and reversal of remodeling of the LV after AMI. Therefore, development of new therapy options is desirable to decrease the incidence of heart failure and to prevent and reverse the remodeling process after AMI.

See page 2270

Several animal experiments (1–3) and, more recently, clinical studies (4–16) have shown that autologous bone marrow cell (BMC) transplantation might improve ventric-

From the Department of Medicine, Division of Cardiology, Pneumology and Angiology, Heinrich-Heine-University of Düsseldorf, Düsseldorf, Germany.
Manuscript received November 14, 2008; revised manuscript received February 18, 2009, accepted February 23, 2009.

ular function and prevent remodeling, when given directly into the infarct-related coronary artery system.

The aim of this study was to investigate the quantitative amount of improvement of ventricular hemodynamic status, geometry, and contractility as well as to explore the long-term (5 years) clinical outcome of treated patients after AMI.

Methods

Study population. A total of 124 patients with AMI were enrolled into the present study. All patients underwent emergency coronary angiography 10 ± 9 h after the onset of the AMI. The infarct-related artery was recanalized by balloon angioplasty and/or stent implantation. Sixty-two patients underwent intracoronary BMC transplantation 7 ± 2 days after the onset of AMI (BMC group). The control group consisted of 62 patients with comparable ejection fraction (EF) and diagnosis. General exclusion criteria were alcohol or drug dependency; acute myocarditis; human immunodeficiency, hepatitis B, or hepatitis C virus infections; pregnancy; and evidence for malignant and hematologic diseases. All patients were treated with aspirin, clopidogrel, beta-blocker, angiotensin-converting enzyme inhibitor (AT2-receptor antagonist), and a diuretic agent (Table 1).

Study design. In 2002 to 2003, the novel kind of BMC therapy was proposed for all patients with AMI 7 ± 2 days after revascularization. Patients that refused the BMC treatment and agreed to undergo all procedures identical to the BMC group acted as the control group. All patients underwent coronary angiography, biplane left ventriculography, right heart catheterization, echocardiography, dobutamine stress echocardiography, late potential (LP), short-term heart rate variability (HRV), electrocardiogram (ECG) at rest, and 24-h Holter ECG. The therapeutic follow-up was performed 3, 12, and 60 months after the treatment (Fig. 1). The present study was approved by the ethic commission of Heinrich-Heine-University of Duesseldorf, Germany.

Abbreviations and Acronyms

AMI = acute myocardial infarction
BMC = bone marrow cell
ECG = electrocardiogram
EDV = end-diastolic volume
EF = ejection fraction
ESV = end-systolic volume
HRV = heart rate variability
LP = late potential
LV = left ventricle/ventricular
SVI = stroke volume index
VCF = velocity of circumferential fiber shortening

Preparation of BMCs. Bone marrow was taken (80 to 120 ml from the iliac crest), and mononuclear cells—including CD34+, CD133+, and CD34− cells—were isolated and identified according to the Paul-Ehrlich criteria under Good Manufacturing Practice. Cells were isolated by Ficoll density separation on Lymphocyte Separation Medium (Bio Whittaker, Walkersville, Maryland), before the residual erythrocytes were lysed with water. The BMCs were washed

Table 1 Baseline Characteristics of BMC and Control Group

Characteristics	BMC Group (n = 62)	Control Group (n = 62)	p Value
Age (yrs)	51.4 ± 10.8	50.7 ± 8.3	NS
BMI (kg/m^2)	26.9 ± 3.7	27 ± 36	NS
Sex (% male)	87.1	92	NS
CKmax (U/l)	1,131 ± 998	1,151 ± 919	NS
EF (%)	51.6 ± 10.6	57.2 ± 10.4	NS
Infarct-related RCA/LAD/RCX (%)	32.6/48.8/18.6	28/52/20	NS
Patients with unplanned hospital stay (%)	14.52	12.9	NS
Patients with repeat PCI (%)	8.06	9.68	NS
Number of injected cells (×10^7)	6.1 ± 3.9	—	
Number of diseased coronary arteries	1.61 ± 0.69	1.6 ± 0.71	NS
Medications (%)			
Aspirin	100	100	NS
Clopidogrel	100	100	NS
ACE-I/angiotensin-II receptor blocker	95	94	NS
Statins	90	91	NS
Beta-blocker	93	92	NS
Cardiovascular risk factors (%)			
Diabetes mellitus	6	5	NS
Hyperlipidemia	94	91	NS
Smoking	52	54	NS
Obesity	60	57	NS
Arterial hypertension	52	49	NS

Sixty-two patients were treated with bone marrow cells (BMCs). The control group consists of 62 patients with comparable ejection fraction (EF); peak creatine kinase (CKmax); diagnosis; body mass index (BMI); and number of diseased coronary arteries, medication, and cardiovascular risk factors. Values are mean ± SD or %.

ACE-I = angiotensin-converting enzyme inhibitor; LAD = left anterior descending coronary artery; PCI = percutaneous coronary intervention; RCA = right coronary artery; RCX = right circumflex coronary artery.

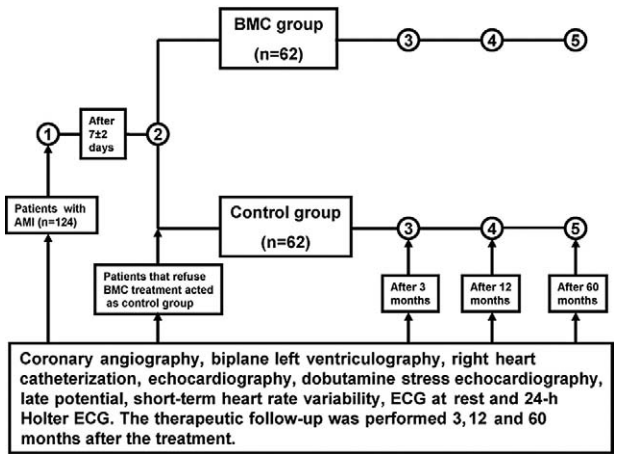

Figure 1 **Study Design**

Sixty-two patients underwent intracoronary bone marrow cell (BMC) transplantation 7 ± 2 days after the onset of acute myocardial infarction (AMI) (BMC group). The control group consisted of 62 patients with comparable ejection fraction and diagnosis. All patients underwent several examinations. The therapeutic follow-up was performed 3, 12, and 60 months after the treatment. ECG = electrocardiogram.

3 times with heparinized saline. Viability was 93 ± 3%. All microbiologic tests of clinically used cell preparations proved negative.

Applications of BMCs. Cells were infused directly into the infarct-related artery via an angioplasty balloon catheter, which was located within the previously stented coronary segment and inflated at a low pressure. The cell transplantation was performed via 4 fractional infusions parallel to balloon inflation over 4 min. Percutaneous transluminal coronary angioplasty (PTCA) thoroughly prevented the backflow of cells and at the same time produced a stop-flow beyond the site of the balloon inflation to facilitate high-pressure infusion of cells into the infarcted zone. Thus, prolonged contact time for cellular migration was allowed (17). To achieve a maximal ischemic stimulus, all patients received dobutamine intravenously and dipyridamol by intracoronary application (18). To ensure a prolonged contact time for cellular adhesion of the mononuclear cells, we additionally applied intracoronary macroalbumin aggregates (19).

Functional assessment of hemodynamic status. Infarct size, EF, regional wall movement, and wall stress of the infarcted zone during ejection were determined by quantitative left ventriculography (Quantcor, version 4.0, Siemens, Erlangen, Germany) that was obtained before coronary angiography (Judkins technique) by intraventricular injection of 20 to 40 ml Ultravist (Bayer Schering Pharma, Berlin, Germany). For each ventriculogram a specific enlargement and aberration factor was taken into account for evaluation and calculation of volumes. The infarct size was calculated according to the method of Sheehan (20). The LV regional function, wall thickness, wall thickness changes, and wall stress were determined in 3 to 4 ventricular wall segments. Perpendicular to the LV longitudinal axis (connecting line between the middle of the aortic valve and the ventricular apex), 3 to 4 vertical axes were established at equal distances (approximately 0.5 cm), and the anterior hemiaxes were drawn. A tangent was drawn to the external ventricular contour in such a way that its perpendicular passed through the intersecting point of the hemiaxis and the interior ventricular contour, thus obtaining ventricular wall segments and distances of approximately centrifugal shape, when seen from a virtual ventricular center. This technique was chosen because, in contrast to other techniques, it helps to prevent or reduce potential overratings of the regional wall thickness, particularly in the basal and apical segments, which otherwise might occur due to distortions in the projection of the outer ventricular contour.

The contractility index LV systolic pressure (P_{syst})/end-systolic volume (ESV) was calculated by dividing P_{syst} by ESV, the velocity of shortening (VCF) as the ratio of shortening/ejection time (mm/s) and the mean normalized systolic ejection rate as the ratio of EF/ejection time (volume/s). An identical methodological procedure was performed for both stem cell and control group patients.

Assessment of arrhythmia. For risk stratification LP, HRV, and 24-h Holter ECG were analyzed. The results of 24-h Holter ECG were listed according to the Lown classification.

Statistical analysis. All data are presented as mean ± SD. Intraindividual comparison of continuous variables at baseline with those at follow-up was performed with the paired *t* test. Comparison of nonparametric data between groups was performed with the Wilcoxon rank sum test and the Mann-Whitney *U* test. Nonparametric correlation was calculated by the Spearman correlation. Statistical significance was assumed at a value of $p < 0.05$. For comparisons of various post-treatment evaluations versus baseline (Table 2), Bonferroni alpha correction was performed and statistical significance was assumed at a value of $p < 0.0167$. Time-dependent mortality rates were estimated by Kaplan-Meier survival curves, and p values were determined by use of log-rank statistics. All statistical analyses were performed with SPSS for windows (version 15, SPSS, Chicago, Illinois).

Results

Baseline characteristics. Clinical data within BMC group and control group did not differ significantly (Table 1). The creatine kinase activity was almost the same, and the initial EF was quantitatively similar. The average of transplanted BMCs in treated patients was $6.1 \pm 3.9 \times 10^7$ cells. In the course of this long-term study the number of patients that received repeat percutaneous coronary intervention and the number of patients with an unplanned hospital stay did not differ significantly between the BMC and the control group.

Table 2 Quantitative Ventriculography Before and 3, 12, and 60 Months After BMC Therapy in Comparison With the Control Group

Parameter	AMI							
	BMC Group				Control Group			
	Baseline (Before BMC Therapy)	After 3 Months	After 12 Months	After 60 Months	Baseline	After 3 Months	After 12 Months	After 60 Months
EDV (ml)								
Mean	150 ± 28	147 ± 29	146 ± 26	147 ± 19	157 ± 19	153 ± 17	160 ± 17	164 ± 21
Abs.	—	−2.7 ± 18.3	−3.9 ± 18	7.2 ± 17.7	—	−3 ± 10	4.9 ± 14.5	11.6 ± 20.2
ESV (ml)								
Mean	73.4 ± 26	60.8 ± 25*	61.1 ± 20*	63.6 ± 18	78.2 ± 25	73.4 ± 20	81.7 ± 24	88.4 ± 24†
Abs.	—	−12.6 ± 10.3	−12.4 ± 11.1	−3.6 ± 13.5	—	−3.1 ± 7.7	6.2 ± 9.7	15.9 ± 14.9
EF (%)								
Mean	51.6 ± 11	59.5 ± 12*	58.3 ± 11*	56.9 ± 9†	50.8 ± 10	52.4 ± 9	49.5 ± 9.3	46.9 ± 8.3†
Abs.	—	7.9 ± 6.9	6.9 ± 7.7	4.6 ± 6.6	—	1 ± 1.98	−2.3 ± 2.7	−5.8 ± 4
SVI (ml/m^2)								
Mean	38.9 ± 10	45.2 ± 11*	43.6 ± 11†	43 ± 8	38.2 ± 10	39 ± 9	37.6 ± 9	36.5 ± 8
Abs.	—	5.45 ± 10.8	4.7 ± 8.7	6.4 ± 6.5	—	0.35 ± 1.84	−1.24 ± 3.5	−6.7 ± 13.9

Values are mean ± SD. Quantitative ventriculography over the course of time after acute myocardial infarction (AMI) in bone marrow cell (BMC) and control group. *$p < 0.0167$ versus baseline (Bonferroni alpha correction); †$p < 0.05$ versus baseline.

Abs. = absolute difference to baseline; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; SVI = stroke volume index.

No differences for pharmacological treatment and cardiovascular risk factors were present (Table 1).

Quantitative ventriculography. Three months after intracoronary BMC transplantation, considerable improvements in the LV performance were observed. The EF improved significantly by 7.9% ($p < 0.01$), and the stroke volume index (SVI) at rest increased by 16.5%. Furthermore, there was a significant decrease in both end-diastolic volume (EDV) and ESV (Table 2). The infarct size was considerably reduced, by 8% (Table 3, Fig. 2). No significant correlation has been documented between the number of injected cells and the infarct size reduction ($p = 0.406$) or the EF improvement ($p = 0.426$).

Contractility of the LV. The LV contractility was determined by several indexes. Contraction velocities (length/s, volume/s) increased, and the contractility index (P_{syst}/ESV) improved significantly (Table 3). The absolute difference in P_{syst}/ESV differed significantly between the 2 patients groups. Over the infarcted region, VCF increased significantly by 31% and the end-systolic wall stress decreased by 8.6% in the BMC group (Table 4).

Arrhythmogenic indexes. In treated patients decreases of abnormal HRV, LP, and ectopic beats were observed (Table 5).

Results 12 and 60 months after cell therapy. After 12 and 60 months deterioration of LV performance occurred in the control group as evidenced by increases in EDV and ESV as well as by decreases in EF (Fig. 3) and SVI (Table 2). In contrast, BMC-treated patients after the initial improvement of ventricular function maintained the improved level

Table 3 Infarct Size and LV Contractility

Parameter	AMI	
	BMC Group	Control Group
MNSER (vol/s)		
Baseline	1.78 ± 0.69	1.8 ± 0.71
After BMC therapy	1.98 ± 0.77*	1.83 ± 0.76
Abs.	1.6 ± 1.5	0.32 ± 0.9
P_{syst}/ESV (mm Hg/s)		
Baseline	1.96 ± 0.82	2.1 ± 0.71
After BMC therapy	2.6 ± 1.2*	2.3 ± 0.81
Abs.	0.65 ± 0.66	0.13 ± 0.33
Infarct size (%)		
Baseline	22 ± 15.4	26 ± 9.4
After BMC therapy	14 ± 11.5*	21 ± 9.1
Abs.	−8.2 ± 9	−5.3 ± 12.9

Infarct size and left ventricular (LV) contractility parameters before and after BMC therapy. *$p < 0.01$ (pre/post).

MNSER = mean normalized systolic ejection rate; P_{syst}/ESV = contractility index calculated by dividing LV systolic pressure (P_{syst}) by ESV; other abbreviations as in Table 2.

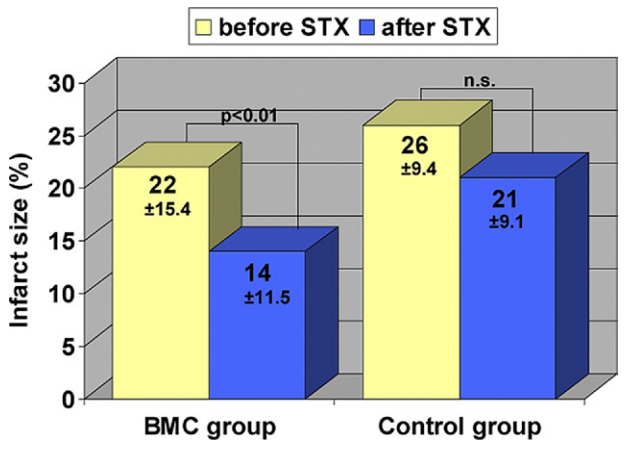

Figure 2 Infarct Size Before and After BMC Therapy in Patients With AMI

Infarct size was significantly reduced in the bone marrow cell (BMC) group. AMI = acute myocardial infarction; STX = stem cell transplantation.

JACC Vol. 53, No. 24, 2009
June 16, 2009:2262–9

Table 4 Regional Ventricular Function

Parameter	AMI			
	BMC Group		Control Group	
	Infarcted	Noninfarcted	Infarcted	Noninfarcted
T-end-systolic ($10^{-3} \times N \times m^2$)				
Baseline	29.2 ± 15.7	8.7 ± 3.5	28.6 ± 14.9	8.3 ± 3.7
After BMC therapy	26.7 ± 14.5*	9 ± 3.6	29.9 ± 15.4	9.8 ± 4.1
Abs.	−2.4 ± 7.9	0.35 ± 1.6	1.3 ± 8.3	0.8 ± 2.1
T-end-diastolic ($10^{-3} \times N \times m^2$)				
Baseline	5.3 ± 2.5	3.8 ± 1.5	5.2 ± 2.4	3.7 ± 1.6
After BMC therapy	5 ± 2.8	3.7 ± 1.6	5.2 ± 2.9	3.8 ± 1.8
Abs.	−0.25 ± 2.7	−0.12 ± 1.7	0.5 ± 1.2	0.15 ± 1.3
VCF (mm/s)				
Baseline	15.9 ± 16.8	47.9 ± 23.3	15.9 ± 14	48.3 ± 24
After BMC therapy	20.9 ± 16.6*	46.3 ± 17.3	15.2 ± 14.2	49.2 ± 23
Abs.	4.9 ± 11.8	−1.7 ± 19.4	−0.7 ± 10.5	0.8 ± 16.3

Improvements of T-end-systolic and wall movement velocity (VCF) were observed 3 months after BMC transplantation in the infarcted area. The VCF, end-diastolic (T-diastolic), and end-systolic wall stress (T-systolic) in the LV infarcted area in comparison with the noninfarcted area in the BMC and control groups. *$p < 0.05$ (pre/post).
Abbreviations as in Table 2.

of performance even after 5 years. Thus, the time course of BMC treatment is characterized by an initial peak improvement (3 months) and an antiremodeling effect (12 and 60 months, respectively) associated with preservation of LV function over time. The absolute difference between baseline and at 3-month follow-up in ESV and EF differed significantly between the BMC and control group.

Mortality. Mortality of BMC-treated patients was significantly reduced in comparison with the control group (all deaths were cardiac deaths). Within a median follow-up time of 4.6 ± 2.1 years in the BMC group, 1 patient died, and of 4.8 ± 2.2 years in the control group, 7 patients died. These numbers are equivalent to average mortality rates of 0.35%/year in the BMC group and of 2.35%/year in the control group ($p = 0.03$). Accordingly, steepness of calculated mortality curves was thoroughly different in treated patients versus control subjects, demonstrating, in terms of Kaplan Meier repression analysis, reduced mortality rates in the treated patient group (Fig. 4).

Table 5 Arrhythmogenic Indexes

Parameter	AMI	
	BMC Group	Control Group
LP: (no. of Simson criteria)		
Baseline	1.67 ± 1.14	1.45 ± 0.98
After BMC therapy	1.56 ± 1.15	1.5 ± 1.02
Abs.	−0.11 ± 0.76	0.5 ± 0.77
HRV: SD of the RR-intervals (ms)		
Baseline	34 ± 17.5	37 ± 15.2
After BMC therapy	48.2 ± 18.8*	33.1 ± 14.2
Abs.	14.2 ± 24.2	−3.5 ± 8.3
Lown class		
Baseline	1.56 ± 1.5	1.43 ± 1.8
After BMC therapy	0.76 ± 0.6*	1.92 ± 1.2
Abs.	−0.8 ± 1.5	0.48 ± 1

Arrhythmogenic indexes before and after BMC therapy. Improvements of late potential (LP), heart rate variability (HRV), and Lown class were observed. *$p < 0.05$ (pre/post).
Abbreviations as in Table 2.

Discussion

The BALANCE (Clinical Benefit and Long-Term Outcome After Intracoronary Autologous Bone Marrow Cell Transplantation in Patients With Acute Myocardial Infarction) study represents the longest available clinical follow-up trial after intracoronary BMC therapy in patients with AMI. The results of the present study are comparable to the clinical outcome data of prior trials (5–16) and meta-

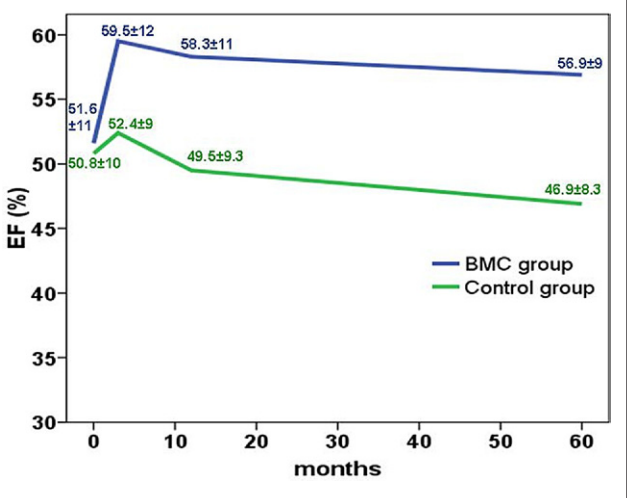

Figure 3 EF Over the Course of Time After BMC Therapy in Patients With AMI in Comparison With the Control Group

Ejection fraction (EF) improves significantly in the bone marrow cell (BMC) group. The initial beneficial effect of BMC therapy, as evidenced by a significant improvement of EF after 3 months, was longstanding after 12 and 60 months. In contrast, the EF decreases in the control group. AMI = acute myocardial infarction.

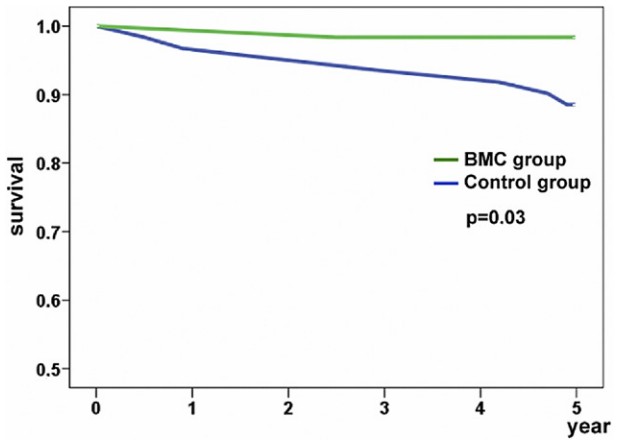

Figure 4 **Mortality in Patients With AMI After BMC Therapy in Comparison With the Control Group**

The mortality of the bone marrow cell (BMC) group was significantly reduced in comparison with the control group. AMI = acute myocardial infarction.

analyses (21–23) employing stem cell therapy after AMI, demonstrating that in infarcted myocardium BMC therapy improves LV hemodynamic (SVI, EF, and the like) (Table 2), LV contractility indexes (VCF [length/s, volume/s]), P_{syst}/ESV (Tables 3 and 4), and LV geometry (decrease in EDV and ESV, decrease in infarct size) (Tables 2 and 3). The contractile behavior of the infarcted myocardium was significantly ameliorated in comparison with the noninfarcted myocardium (Table 4). Moreover, intracoronary BMC therapy also was associated with other beneficial effects, such as improvement of LP and HRV (Table 5). Another important result refers to the considerable decrease in mortality of treated patients over a median follow-up time of 4.6 ± 2.1 years (Fig. 4).

Ideal time point of BMC application. In the present study, the time point of BMC transplantation was 7 ± 2 days after the onset of the AMI, because the infarct-related inflammatory process is strongest in the first 5 days after AMI and, therefore, immediate BMC transplantation is not advisable (24). However, 2 weeks after AMI, beginning scar formation might reduce the beneficial effects of BMCs (25,26). Therefore, the ideal time point for BMC transplantation is most likely between 5 and 14 days after the onset of AMI.

Regional LV function. When analyzing regional LV function, the contractile improvement was predominant within the infarcted area, whereas the noninfarcted muscle was almost unchanged. Regional VCF increased significantly by 31% within the infarcted area, whereas the noninfarcted area was unaffected. This result might underline the importance of the border zone for BMC-associated repair of the infarcted myocardium, because regeneration of blood vessels and muscle cells is most pronounced in the border zone of infarcted tissue.

This considerable increase in VCF reflects a BMC-related increase in contractility within the infarct zone and/or the border zone. Changes of VCF are not only due to changes in contractility but also, in part, to altered load factors of the heart (preload, afterload). However, VCF related to systolic wall stress (i.e., to the force/cross-sectional area of the LV wall) shows that, per given systolic wall stress, the VCF is increased after BMC therapy. This implies that the formerly (before BMC therapy) avital and low or noncontractile tissue has regenerated contractile properties again, by regeneration of new myocytes or by contractile improvement of diseased myocytes within the border zone or by both. The noninfarcted myocardial tissue was unchanged with regard to VCF and systolic stress, indicating again the importance of the border zone for regeneration of infarcted myocardium.

BMC effects versus spontaneous healing and remodeling. The persistent beneficial effects over the follow-up time justify the assumption that BMC treatment might overcome the possibly detrimental effects of ventricular remodeling. Remodeling after myocardial infarction represents a major cause of infarct-related heart failure and death. This process depends on acute and chronic transformation of both the necrotic infarct region and the non-necrotic, peri-infarct tissue (27). Remodeling is difficult to quantify; however, it occurs in approximately 60% of cardiac patients after myocardial infarction (28).

The infarct size is a major determinant of ventricular remodeling and determines the likelihood of late remodeling after myocardial infarction (29). Several studies have demonstrated a benefit from myocardial reperfusion by an opened infarct-related artery, resulting in reduced infarct size and in improvement of late regional and global ventricular function (30,31). The present study demonstrates that reduction of infarct size is associated with an improvement in LV function. The values (e.g., LVEF, infarct size) of control patients, although nonsignificant, might reflect a certain spontaneous healing. In contrast, the BMC group exhibits a considerable and highly significant decrease in infarct size, which also goes parallel to the improved LV performance (LVEF). Thus, even when taking a certain amount of spontaneous healing—as in AMI—into account, there is enough evidence for beneficial BMC-related effects that become manifest in addition to the conventional therapeutic procedure. In contrast, the apersistent beneficial effects over the long follow-up time justify the assumption that BMC treatment might overcome the possibly detrimental effects of ventricular remodeling.

Mortality after intracoronary BMC transplantation. The present study demonstrated considerable and significant reduction of mortality in the BMC group in comparison with the control group ($p = 0.03$).

Other factors (e.g., repeat PTCA, stent implantation, aortocoronary venous bypass) that might influence clinical benefit or mortality after a new treatment have to be considered. However, the percentage of repeat PTCA and

of aortocoronary venous bypass was not different between the BMC and the control group, demonstrating that these non–BMC-related procedures most probably do not interfere with the beneficial results obtained by BMC treatment.

Furthermore, when comparing the mortality rates from this study with mortality rates of other studies containing comparable diagnoses and equivalent hemodynamic status, it becomes evident that mortality of 1.6% 5 years after AMI has not been reported until now in the published reports that analyze long-term mortality or survival in patients with AMI (mortality 13% to 24% after 5 years) (32).

The reason for long-term survival in the BMC group might be due primarily to a decrease of 2 of the main reasons for deaths in patients with coronary artery disease (i.e., decrease in pump failure and severe cardiac arrhythmias).

A decrease in the occurrence of heart failure after BMC therapy might be related to the contractile and antiremodeling action of BMCs in the infarcted myocardium. This study has shown a broad spectrum of improved functional variables, including improved conditions (e.g., decrease in systolic wall stress), increased myocardial contractility (e.g., VCF), enhanced ventricular power (as reflected, for example, by LV power index and by ratio P_{syst}/ESV) and—as the consequence of these variables—an improvement of the overall and regional ventricular performance. Because these effects are persistent over years, it is reasonable to assume that they are the basis for the long-lasting antifailing property of BMC therapy in patients with AMI. BMC therapy seems to exert structural effects in the sense that remodeling might be prevented or delayed, thereby enabling the heart for better overall performance. The second main reason for the decrease in mortality in the BMC-treated patients refers to cardiac arrhythmias. There is good evidence that an impaired LV function increases malignant ventricular arrhythmias and predisposes for sudden cardiac death. Large studies concerning the spontaneous course of ischemic cardiomyopathy demonstrate an incidence of 20% to 30%/year of sudden cardiac death induced by malignant ventricular arrhythmias after AMI. All treated patients in this study revealed no malignant arrhythmias, and there was evidence for a decreased arrhythmogenic risk as shown by the improvement of HRV and LP. It is likely that decreased arrhythmogenic risk in BMC-treated patients obtains its hemodynamic equivalent by the BMC-induced antiremodeling properties, with improvement in LV function.

Conclusions and Clinical Perspective

Medical treatment or revascularization after AMI can improve the function of viable or hibernating myocardium but cannot restore necrotic myocardial tissue. Current therapy strategies are limited in prevention and reversal of LV remodeling after AMI. Consequently, therapeutic regimens are desirable, which alternatively or in addition to conventional therapy might improve ventricular performance and increase survival after AMI.

The results of the present study demonstrate that BMC therapy represents a novel and effective therapeutic procedure for the repair of infarcted myocardium and offers a new possibility for the treatment after AMI. The long-term survival analysis shows that BMC therapy reduces mortality in treated patients. In the long-term follow-up no side effects of BMC therapy were observed, demonstrating that BMC therapy is safe. Because of the relatively small sample size of the BALANCE study, further studies with greater sample size are required to confirm the findings of the present study and to determine which cell biological and molecular mechanisms are responsible for heart muscle repair as well as to clarify which is the ideal mode of cell preparation technique and application.

Reprint requests and correspondence: Dr. Muhammad Yousef, Department of Medicine, Division of Cardiology, Pulmonary Disease and Angiology, Heinrich-Heine-University of Düsseldorf, Moorenstrasse 5, 40225 Düsseldorf, Germany. E-mail: muhammad.yousef@med.uni-duesseldorf.de.

REFERENCES

1. Shamblott MJ, Axelman J, Wang S, et al. Derivation of pluripotent stem cells from cultured human primordial germ cells. Proc Natl Acad Sci U S A 1998;95:13726–31.
2. Orlic D, Kajstura J, Chimenti S, Bodine DM, Leri A, Anversa P. Transplanted adult bone marrow cells repair myocardial infarcts in mice. Ann N Y Acad Sci 2001;938:221–9.
3. Fuchs S, Baffour R, Zhou YF, et al. Transendocardial delivery of autologous bone marrow enhances collateral perfusion and regional function in pigs with chronic experimental myocardial ischemia. J Am Coll Cardiol 2001;37:1726–32.
4. Strauer BE, Brehm M, Zeus T, et al. Regeneration of human infarcted heart muscle by intracoronary autologous bone marrow cell transplantation in chronic coronary artery disease: the IACT Study. J Am Coll Cardiol 2005;46:1651–8.
5. Strauer BE, Brehm M, Zeus T, et al. [Intracoronary, human autologous stem cell transplantation for myocardial regeneration following myocardial infarction]. Dtsch Med Wochenschr 2001;126:932–8.
6. Strauer BE, Brehm M, Zeus T, et al. Repair of infarcted myocardium by autologous intracoronary mononuclear bone marrow cell transplantation in humans. Circulation 2002;106:1913–8.
7. Assmus B, Schachinger V, Teupe C, et al. Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction (TOPCARE-AMI). Circulation 2002;106:3009–17.
8. Schachinger V, Erbs S, Elsasser A, et al. Improved clinical outcome after intracoronary administration of bone-marrow-derived progenitor cells in acute myocardial infarction: final 1-year results of the REPAIR-AMI trial. Eur Heart J 2006;27:2775–83.
9. 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;364:141–8.
10. Chen SL, Fang WW, Ye F, et al. Effect on left ventricular function of intracoronary transplantation of autologous bone marrow mesenchymal stem cell in patients with acute myocardial infarction. Am J Cardiol 2004;94:92–5.
11. Meluzin J, Mayer J, Groch L, et al. Autologous transplantation of mononuclear bone marrow cells in patients with acute myocardial infarction: the effect of the dose of transplanted cells on myocardial function. Am Heart J 2006;152:975–15.
12. Lunde K, Solheim S, Aakhus S, et al. Intracoronary injection of mononuclear bone marrow cells in acute myocardial infarction. N Engl J Med 2006;355:1199–209.
13. Tatsumi T, Ashihara E, Yasui T, et al. Intracoronary transplantation of non-expanded peripheral blood-derived mononuclear cells pro-

motes improvement of cardiac function in patients with acute myocardial infarction. Circ J 2007;71:1199–207.
14. Li ZQ, Zhang M, Jing YZ, et al. The clinical study of autologous peripheral blood stem cell transplantation by intracoronary infusion in patients with acute myocardial infarction (AMI). Int J Cardiol 2007; 115:52–6.
15. Kang HJ, Kim HS, Koo BK, et al. Intracoronary infusion of the mobilized peripheral blood stem cell by G-CSF is better than mobilization alone by G-CSF for improvement of cardiac function and remodeling: 2-year follow-up results of the Myocardial Regeneration and Angiogenesis in Myocardial Infarction with G-CSF and Intra-Coronary Stem Cell Infusion (MAGIC Cell) 1 trial. Am Heart J 2007;153:237–8.
16. Schachinger 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;44:1690–9.
17. Wang JS, Shum-Tim D, Chedrawy E, Chiu RC. The coronary delivery of marrow stromal cells for myocardial regeneration: pathophysiologic and therapeutic implications. J Thorac Cardiovasc Surg 2001;122:699–705.
18. Heidland UE, Heintzen MP, Schwartzkopff B, Strauer BE. Preconditioning during percutaneous transluminal coronary angioplasty by endogenous and exogenous adenosine. Am Heart J 2000;140:813–20.
19. Felix R, Pensky W, Wagner J, et al. [Selective coronary-artery perfusion imaging with radioactive labelled particles (author's transl)]. Dtsch Med Wochenschr 1974;99:2258–61.
20. Sheehan FH, Bolson EL, Dodge HT, Mathey DG, Schofer J, Woo HW. Advantages and applications of the centerline method for characterizing regional ventricular function. Circulation 1986;74:293–305.
21. 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;50:1761–7.
22. Hristov M, Heussen N, Schober A, Weber C. Intracoronary infusion of autologous bone marrow cells and left ventricular function after acute myocardial infarction: a meta-analysis. J Cell Mol Med 2006; 10:727–33.
23. 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;167:989–97.
24. Sheiban I, Fragasso G, Rosano GM, et al. Time course and determinants of left ventricular function recovery after primary angioplasty in patients with acute myocardial infarction. J Am Coll Cardiol 2001;38:464–71.
25. Frangogiannis NG, Smith CW, Entman ML. The inflammatory response in myocardial infarction. Cardiovasc Res 2002;53:31–47.
26. Li RK, Mickle DA, Weisel RD, Rao V, Jia ZQ. Optimal time for cardiomyocyte transplantation to maximize myocardial function after left ventricular injury. Ann Thorac Surg 2001;72:1957–63.
27. Pfeffer MA, Braunwald E. Ventricular remodeling after myocardial infarction. Experimental observations and clinical implications. Circulation 1990;81:1161–72.
28. St. John SM, Pfeffer MA, Moye L, et al. Cardiovascular death and left ventricular remodeling two years after myocardial infarction: baseline predictors and impact of long-term use of captopril: information from the Survival and Ventricular Enlargement (SAVE) trial. Circulation 1997;96:3294–9.
29. Sutton MG, Sharpe N. Left ventricular remodeling after myocardial infarction: pathophysiology and therapy. Circulation 2000;101: 2981–8.
30. Touchstone DA, Beller GA, Nygaard TW, Tedesco C, Kaul S. Effects of successful intravenous reperfusion therapy on regional myocardial function and geometry in humans: a tomographic assessment using two-dimensional echocardiography. J Am Coll Cardiol 1989;13: 1506–13.
31. Marino P, Zanolla L, Zardini P. Effect of streptokinase on left ventricular modeling and function after myocardial infarction: the GISSI (Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico) Trial. J Am Coll Cardiol 1989;14:1149–58.
32. Zijlstra F, Hoorntje JC, de Boer MJ, et al. Long-term benefit of primary angioplasty as compared with thrombolytic therapy for acute myocardial infarction. N Engl J Med 1999;341:1413–9.

Key Words: acute myocardial infarction ■ intracoronary cell therapy ■ remodeling.