Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 58, No. 11, 2011
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.06.016

STATE-OF-THE-ART PAPER

10 Years of Intracoronary and Intramyocardial Bone Marrow Stem Cell Therapy of the Heart

From the Methodological Origin to Clinical Practice

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Intracoronary and intramyocardial stem cell therapy aim at the repair of compromised myocardium thereby—as a causal treatment—preventing ventricular remodeling and improving overall performance. Since the first-in-human use of bone marrow stem cells (BMCs) after acute myocardial infarction in 2001, a large number of clinical studies have demonstrated their clinical benefit: BMC therapy can be performed with usual cardiac catheterization techniques in the conscious patient as well as also easily during cardiosurgical interventions. New York Heart Association severity degree of patients as well as physical activity improve in addition to ("on top" of) all other therapeutic regimens. Stem cell therapy also represents an ultimate approach in advanced cardiac failure. For acute myocardial infarction and chronic ischemia, long-term mortality after 1 and 5 years, respectively, is significantly reduced. A few studies also indicate beneficial effects for chronic dilated cardiomyopathy. The clinical use of autologous BMC therapy implies no ethical problems, when unmodified primary cells are used. With the use of primary BMCs, there are no major stem cell-related side effects, especially no cardiac arrhythmias and inflammation. Various mechanisms of the stem cell action in the human heart are discussed, for example, cell transdifferentiation, cell fusion, activation of intrinsic cardiac stem cells, and cytokine-mediated effects. New techniques allow point-of-care cell preparations, for example, within the cardiac intervention or operation theater, thereby providing short preparation time, facilitated logistics of cell transport, and reasonable cost effectiveness of the whole procedure. The 3 main indications are acute infarction, chronic ischemic heart failure, and dilated cardiomyopathy. Future studies are desirable to further elucidate the mechanisms of stem cell action and to extend the current use of intracoronary and/or intramyocardial stem cell therapy by larger and presumably multicenter and randomized trials. (J Am Coll Cardiol 2011;58:1095–104) © 2011 by the American College of Cardiology Foundation

Just over 10 years ago, on March 30, 2001, autologous unfractionated mononuclear bone marrow stem cells (BMCs) were used for the first time in the clinical treatment of the failing left ventricle after acute myocardial infarction in a 46-year-old patient by intracoronary application (1). On July 3, 2001, the first intramyocardial application of a purified ($CD133^+$) BMC preparation was applied to a 64-year-old patient with heart failure after myocardial infarction during a coronary artery bypass graft (CABG) operation starting a phase I trial (2). These early clinical steps prompted a series of subsequent studies of acute and chronic heart diseases, for example, in acute myocardial infarction, in chronic cardiac failure, and in dilated cardiomyopathy (DCM) (3–11). In the following overview, methodological and clinical prerequisites of cardiac cell therapy and cell preparation procedures are described, including the experience with different cell application methods; it summarizes recent results of currently available clinical studies investigating the safety, feasibility, and efficacy of this new kind of regenerative cell therapy in heart disease.

Remodeling

In acute myocardial infarction, heart muscle tissue is regionally destroyed. By the sum of CABG surgery and percutaneous coronary intervention (PCI), regular heart muscle function may not be restored or only to a minor degree, so that remodeling, which may occur in approximately 60% of the patients after myocardial infarction, is mostly not prevented (12–14). It is estimated that left ventricular ejection fraction (LVEF) is improved after PCI by approximately 3% to 4% only (15). Conversely, cell therapy—as a causal treatment of myocardial hypoperfusion and cell

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Manuscript received March 4, 2011; revised manuscript received April 6, 2011, accepted April 7, 2011.

JACC Vol. 58, No. 11, 2011
September 6, 2011:1095–104

Abbreviations and Acronyms

BMC = bone marrow stem cell

CABG = coronary artery bypass graft

DCM = dilated cardiomyopathy

LVEF = left ventricular ejection fraction

PCI = percutaneous coronary intervention

PTCA = percutaneous transluminal coronary angioplasty

loss—has the fundamental aim to prevent remodeling by reconstitution of perfusion, thereby leading to myocardial functional recovery. That occurs preferably in addition to ("on top" of) all usual pharmacotherapeutic regimens available for symptomatic treatment of ischemic heart failure.

BMCs for Cardiac Repair

Various stem cell or progenitor cell containing populations have been introduced for cardiac repair in the last few years, although many past and ongoing clinical trials use predominantly adult autologous BMCs (16–18). The BMCs contain several cell populations that have the capacity to proliferate, migrate, and also differentiate into various mature cell types. Among these cells are hematopoetic stem cells (19–32), mesenchymal stem cells (33–40), endothelial progenitor cells (41–43), and side population cells (44,45). In brief, human adult bone marrow contains a variety of regenerative autologous precursor/progenitor cells that enhance cardiac performance. The use of BMC in cardiovascular diseases has the advantage that bone marrow can be easily accessed, is renewable, and is an autologous source for regenerative cells. The use of purified and selective expanded cell populations may allow a more specific cardiac stem cell therapy in the future.

Preparation of autologous BMCs for cardiac therapy. Important prerequisites for clinical cell therapy are the precise and careful preparation of the cells harvested from the adult bone marrow, the concentration of high cell numbers within the infarction, predominantly in the ischemic border zone, an enhanced migration of stem cells into the apoptotic and necrotic myocardial tissue, and the homing of the injected cells in the damaged myocardium, to avoid the recirculation loss of the injected cells to bone marrow, spleen, liver, and lungs.

For cell therapy, 80 to 250 ml adult bone marrow blood is aspirated from the iliac crest under local anesthesia. In the past, the mononuclear fraction of cells was separated from the whole bone marrow aspirate by density gradient centrifugation using osmolaric media such as ficoll or gelatineolysuccinate (3,4,46,47). However, both methods comprise open preparation procedures and need several washing steps; thus, both techniques need a good manufacturing practice process to produce a quality-controlled cell product and avoid contamination of the end product (48,49). That is especially mandatory for further processing of CD133 or CD34 purification of stem cells (2). Furthermore, both manual preparation protocols take at least 4 h. During cell preparation, viability needs to be determined several times, and finally must reach approximately 95%. Cell product characterization by fluorescence-activated cell sorting or a cell counter is needed for individual release.

Recently, several new automatic systems were developed to gain nucleated or mononuclear cells from the whole bone marrow aspirate. The advantage of such systems is the possibility to separate the cells in a closed system. In these systems, the cell recovery is higher than with manual preparation (50), and with the same functional capabilities (51). Additionally, the preparation time is definitely shorter. The cell preparation and cell application can be done in 1 working process, which is considerably cheaper than the conventional BMC preparation procedures. Nowadays, 3 different separation strategies exist: 1) separation of the total nucleated cells from the bone marrow aspirate (50); 2) separation of the mononuclear cell fraction (51); and 3) purification selection of specified stem cells including CD34 or CD133 cells (52).

Most of these automatic separation systems separate different cell populations. Therefore, the clinical specialist has to decide which system fits best for the chosen application and cardiovascular setting. Furthermore, a consensus has to be reached to establish a standard protocol for characterization and testing of transplantation products in cardiovascular setting and a standard quality of the final cell product.

Cell delivery to the heart. One of the most important and crucial methodologic questions refers to the optimum mechanism of cell delivery to the heart (53,54). When given intravenously, only a very small fraction of infused cells can reach the infarct region; assuming normal coronary blood flow of 80 ml/min/100 g intravenous weight, a quantity of 160 ml per left ventricle (assuming a regular ventricular mass of 200 g) will flow per minute. This corresponds to approximately 3% of cardiac output (assuming a cardiac output of 5,000 ml/min) (55,56). Thus, intravenous application would require many circulation passages to enable infused cells to come into contact with the infarct-related artery. Throughout this long circulation and recirculation time, homing of cells to other organs could considerably reduce the number of cells dedicated to cell repair in the area of interest, namely, in the infarcted zone. Therefore, homing of stem cells to cardiac ischemic tissue from the circulation, as shown by Ma et al. (57), has to be considered a physiological process with restricted efficiency (58–63). Clinical evaluation of homing to infarcted myocardium with 18-fluorodeoxyglucose labeling of unselected BMC has revealed a cardiac retention of 1.3% to 2.6% after intracoronary application (58). The current principles of clinically employed cell delivery methods are depicted in Figure 1 (64).

Intracoronary application. Supplying the entire heart muscle compartment by intracoronary cell administration obviously seems to be advantageous for tissue repair of infarcted heart muscle after interventional reopening of the occluded coronary artery. Cells are able to flow through the infarcted and peri-infarct tissue during the immediate first passage of the post-ischemic region. Accordingly, by this intracoronary procedure the infarct tissue and the peri-

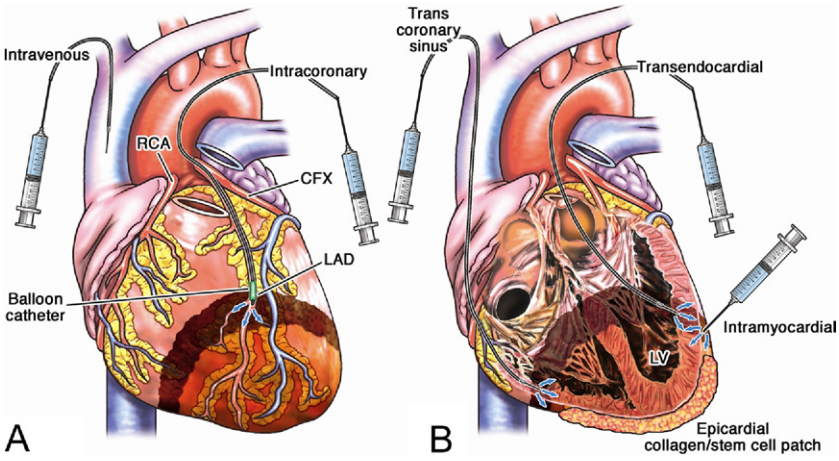

Figure 1 **Various Transplantation Methods in Heart Disease**

(A) Intracoronary and **(B)** intramyocardial transplantation methods in heart disease. Depicted are clinically used methods for vascular and myocardial cell delivery in cardiac intervention and cardiac surgery. CFX = circumflex artery; LAD = left anterior descending artery; LV = left ventricle; RCA = right coronary artery.

infarct zone can be enriched depending on the arterial circulation access of the tissue compartments.

A selective intracoronary delivery route, therefore, has been developed clinically (1) that minimizes the cell loss due to extraction toward organs of secondary interest by this first-pass–like effect. To facilitate transendothelial passage and migration into the infarct zone, cells are infused by pressure injection directly into the perinecrotic tissue accompanied by ischemic pre-conditioning. This is accomplished by a balloon catheter-induced ischemia, which is placed within the infarct-related artery. After exact positioning at the site of the former infarct vessel occlusion, percutaneous transluminal coronary angioplasty (PTCA) is performed. During this time of vessel occlusion, cells are infused intracoronarily through the balloon catheter, using 4 fractional high-pressure infusions of 5 ml cell suspension, each of which contains 6 to 10 million mononuclear cells. The PTCA thoroughly prevents backflow of cells and at the same time produces a stop flow beyond the site of balloon inflation to facilitate migration of cells into the infarcted zone. Thus, prolonged contact time for cellular migration is allowed, and cells are not washed away immediately under these conditions. This migration process is probably only present in injured and ischemic tissue (59). The induction of stem cell specific adhesion molecules in the late phase after ischemia-reperfusion injury seems to be the crucial step for stem cell homing and is relevant for the timing of stem cell therapy (59).

Endocardial intramyocardial application. A second interventional delivery route for cardiac stem cell transplantation is the transendocardial catheter injection (58), preferably using the NOGA injection catheter (Biosense Webster Ltd., Diamond Bar, California), which is placed across the aortic valve into the target area (65,66). This interventional approach offers intramyocardial cell delivery similar to the surgical approach with being less invasive at the same time. The first clinical studies were able to prove safety and feasibility of the transendocardial route in the setting of chronic ischemic heart disease (65) as well as for intractable angina (66). However, orientation by electromechanical mapping is technically demanding, and cell loss into the ventricle, wrong injections sites, ventricular arrhythmias, and cardiac tamponade can occur.

Epicardial intramyocardial application. Surgical (epicardial) stem cell application is performed into well-exposed ischemic areas, allowing for multiple injections within and principally around the infarct area with a thin needle. First clinical studies performed stem cell injection in combination with CABG (2). Once the graft–coronary artery anastomosis is completed, the ischemic area is visualized, and the cells are injected into the border zone of the infarcted area (2,9,67).

This method has been applied successfully also during off-pump coronary artery bypass grafting as well as a stand-alone minimally invasive procedure in which cell injection is performed without cardiac arrest. As with the transendocardial cell delivery, intramyocardial stem cell injection during surgery seems to overcome the problem linked to insufficient vascularization, migration, and homing of transplanted stem cells more likely than to the attempts to influence stem cell migration process in the vasculature and results in a high stem cell persistence in heart muscle (67). Recent reports about surgical stand-alone stem cell therapy are of great interest (60,68,69). Therein, patients improved in myocardial perfusion and clinical symptoms as a result of stem cell injection only through lateral minithoracotomy. Besides distinguishing between stem cell and revascularization effects on cardiac function, this approach

could help to further minimize perioperative risks in the context of surgical stem cell therapy.

Mechanisms of stem cell action in the diseased heart. The regenerative potential of bone marrow-derived stem cells may be explained by at least any of 4 mechanisms: 1) direct cell transdifferentiation from BMCs to cardiac myocytes (19,70); 2) cytokine-induced myocyte growth (18,23) and increase of residual viable myocytes (especially in the border zone of the infarcted area); 3) stimulation of intrinsic myocardial stem cells (endogenous stem cells) (18); and 4) induction of cell fusion between transplanted BMCs and resident myocytes (71,72), which was taken as an explanation for transdifferentiation.

The influence of cytokines has been shown to restore coronary blood vessels and muscle cells after experimental infarction by angiogenesis. Bone marrow stem cells express a bounty of cytokines (e.g., vascular endothelial growth factors, insulin-like growth factor, platelet-derived growth factor), thereby stimulating residual normal myocytes for regeneration (31,71,73) and proliferation, and intrinsic myocardial stem cells (endogenous stem cells) for cell regeneration and fusion.

The importance of ischemic pre-conditioning. Stromal-derived factor-1 and its receptor CXCR4 are well established to be essential for the enhancement of hematopoetic progenitor cell recruitment and angiogenesis (60–63). The expression of stromal-derived factor-1 is up-regulated during acute ischemia and stimulates the CXCR4 receptor, which is expressed on endothelial progenitor cells and BMCs, thereby acting as a chemotactic and promigratory factor. Currently, it is not known how many cells are exactly retained in the myocardium after intracoronary infusion and migrate into the border zone. Because myocardial ischemia may be an appropriate stimulus for a stem cell to find its optimum myocardial niche, the ischemia-producing stimulus, for example, by balloon dilation during the BMC infusion (ischemic pre-conditioning), seems to be important for the cells to home into the cardiac endothelium (49,57,74). It is obvious that cells may pass through the coronary vascular bed without significantly enhanced homing to coronary endothelium when only injected into the coronary arteries without pre-conditioning interventions. With respect to obvious differences in the intracoronary delivery techniques used in various publications, the variable outcome of results and therapeutic efficiency may be due to the nonstandardized mode of BMC infusion into the coronary circulation. Precise methodological standardization seems to be relevant for both effectiveness of stem cell therapy in clinical heart disease and the comparability of multicenter stem cell studies (49,57,74).

Cell therapy in the elderly cardiac patient. With aging, there is an increase in the incidence and severity of ischemic cardiovascular diseases. Pharmacotherapeutical regimen as well as revascularization therapy, such as PTCA or CABG, are not sufficient to bring about an improvement of a widely impaired cardiac function. However, it has been suggested that therapeutic stem cell application may offer hope for these severely ill patients (75), although some data suggest that cell therapy may have only a limited effect in the elderly, because of the physiological changes that have occurred in the aged myocardium, and by the aged (autologous) stem cells themselves.

For elderly patients who remain symptomatic despite intensive medical treatment, autologous BMCs represent a very promising attempt to repopulate lost myocardial tissue. To intensify the benefit of the autologous stem cell application in the elderly: 1) an increased extraction of bone marrow blood and cell number; 2) a pre-treatment of the bone marrow-derived mononuclear cells with specific growth factors in vitro; 3) the injection of a higher amount of regenerative cells; and 4) enhanced ischemia of the myocardium induced by prolonged intracoronary balloon dilation will all have to be considered for treatment improvement in the future. Therapy with BMCs is ethically justified for treatment of patients of all ages.

Clinical Results and Indications

Acute myocardial infarction. In acute myocardial infarction, a variety of studies have demonstrated longstanding (up to 3 years and more) improvement of ventricular performance after using stem cell therapy, resulting in an increase in ejection fraction by 3% to 36% (mean 11.4%) and decreased infarct size by 1% to 60% (mean 34%) (Table 1) (1,3–5,32,76). In most studies, stem cell transplantation was performed in a time frame of 8 to 14 days after infarction. Although large variability of hemodynamic data after cell therapy exists (Table 1), there is moderate, but unequivocal improvement of performance of the infarcted heart after stem cell therapy that is quantitatively more than the sum of the interventional measures (PTCA, stent) and may be achieved in addition to these therapeutic interventions and to pharmacotherapy (4,46). Thus, autologous stem cell therapy represents an innovative and effective procedure for regeneration of impaired heart muscle in the early phase after the infarct (3–5,32,46,77–88).

The reason for the large variety of stem cell effects and for minor or negative results in some studies may be stem cell-related or dependent on different methods for the heart's functional evaluation: for example, by: 1) different methodology of cell preparations associated with altered cell viability; 2) various ages of patients with age-dependent loss of cell viability; 3) nonstandardized cell delivery to the heart, especially of the intensity of ischemic pre-conditioning during cell transfer, which represents an important prerequisite for ischemia-induced cell migration; 4) various amount of delivered cells; 5) different times between the acute infarct and stem cell therapy; and 6) noncalculable access to the border zone between the infarct and unaffected tissue because of vessel occlusion or nonsufficient intracoronary cell delivery. Moreover, methods for the assessment of ventricular function and perfusion (ventriculography, echo-

Table 1 Landmark Trials of Intracoronary and Intramyocardial Stem Cell Therapy in Acute and Chronic Ischemic Heart Disease

First Author/Study (Ref. #) (Type of Study)	n	Cell Application After AMI	Application Cell Type	Number of Cells	Results	Method
Stem Cell Therapy in Acute Myocardial Infarction						
Strauer 2001 (1) (C)	1	6 days	BMC	12×10^6	EF +16%	GBP
					Cardiac index +30%	GBP
					Infarct size −36%	SPECT
Strauer 2002 (3) (C)	20	7–9 days	BMC	28×10^6	EF +9%	LV angiogram
	1:1 vs. control				Infarct size −60%	LV angiogram
TOPCARE-AMI (4) (C)	59	4–6 days	Circ. Prog.	16×10^6	EF +16%	LV angiogram
			BMC	213×10^6	ESV −25%	LV angiogram
Chen (97) (C)	69	18 days	MSC from bone marrow		EF +36%	LV angiogram
	1:1 vs. control				ESV −53%	LV angiogram
					Infarct size −60%	
BOOST (5) (R)	60	4–6 days	BMC vs. rand. controls	$2{,}460 \times 10^6$	EF +13%	MRI
	1:1 rand.				ESV −2%	MRI
					Infarct size −43%	MRI
Janssens (6) (R)	67	<24 h	BMC vs. i.c. placebo	304×10^6	EF +7%	MRI
	1:1 rand. placebo, double-blind				ESV −3%	MRI
					Infarct size −50%	MRI
BALANCE (32) (R)	124	7 days	BMC vs. rand. controls	6.1×10^7	EF +4.6%	LV angiogram
					ESV −3.6 ml	LV angiogram
					Infarct size −8.2%	LV angiogram
TACT-PB-AMI (83) (R)	54	3 days	PBSC	5×10^9	EF +13%	LV angiogram
Cardiac Study (84) (R)	38	4 days	BMC vs. rand. controls	41.8×10^7	EF +13.1%	SPECT
REGENT (85) (R)	200	3–12 days	BMC	178×10^6	EF +3%	MRI
			CD34+CXCR4+	1.9×10^6	EF +3%	MRI
BONAMI (87) (R)	100	7–10 days	BMC vs. rand. controls	98×10^6	BMC, EF +4.3%	SPECT
					Controls, EF +3.3%	SPECT
ASTAMI (89) (R)	100	6 days	BMC vs. rand. controls	87×10^6	EF +1.9%	SPECT
	1:1 rand.				Infarct size −25%	SPECT
REPAIR-AMI (46) (R)	204	4 days	BMC vs. i.c. placebo	$>230 \times 10^6$	EF +11%	LV angiogram
	1:1 rand. placebo, double-blind				ESV −1%	LV angiogram
Chronic Ischemic Heart Disease						
Strauer (7) (C)	36	3 months to	BMC	28×10^6	EF +15%	LV angiogram
	1:1 vs. controls	9 yrs			Infarct size −30%	LV angiogram
TOPCARE-CHD (89) (R)	75	>3 months				
	BMC group		BMC	205×10^6	EF +7% (BMC)	LV angiogram
	Circ. prog. group		Circ. prog.	22×10^6	ESV, infarct size −4%	LV angiogram
	Control group		No infusion			LV angiogram
STAR (97) (C)	391	8.5 ± 3.2 yrs	BMC	6.6×10^7	EF +6.7%	LV angiogram
					ESV −18 ml	LV angiogram
					Infarct size −4.5	LV angiogram

The percent changes (+/−) refer to the percent change of parameter before and after cell therapy.

BMC = bone marrow stem cell; C = controlled study; Circ. prog. = circulating progenitor cells; EF = ejection fraction; ESV = end-systolic volume; GBP = gated blood pool; i.c. = intracoronary; LV = left ventricular; M = meta-analysis; MRI = magnetic resonance imaging; MSC = mesenchymal stem cells; PBSC = peripheral blood stem cell(s); R = randomized study; rand. = randomized; SPECT = single-positron emission computed tomography.

cardiography, magnetic resonance imaging, single-positron emission computed tomography) are often not comparably used. This variability of methods probably may lead to nonuniform and nonstandardized cell availability to the damaged area of interest and may impede the comparability of data of various trials. Therefore, exact and comparable methodology of cell preparation, of cell delivery, and of the clinical patient selection and procedures are necessary.

Chronic infarction/ischemic heart disease. To date, several clinical studies have revealed beneficial stem cell effects in subacute and chronic ischemic heart failure (Table 1). Surgical studies have also been designed for this setting (Table 2) (90–92). Combined with CABG, the improvement of cardiac function by the use of BMCs has been described as an increase in LVEF of approximately 10% (2,67,93,94). Studies combining stem cell transplantation with off-pump coronary surgery report similar results (95), implicating that cardiac arrest is not mandatory for safe and efficient stem cell implantation. However, these results will always be difficult to interpret conclusively without consideration of revascularization effects. Therefore, recent reports about "stand-alone stem cell treatment" for patients with

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Table 2 Landmark Trials of Epicardial Intramyocardial Stem Cell Therapy in Ischemic Heart Disease

First Author/Study (Ref. #) (Type of Study)	n	Cell Application After AMI	Application Cell Type	Number of Cells	Results	Method	
Stem Cell Therapy in Ischemic Heart Disease							
Stamm (9) (R)	40	Median 9 weeks	CD133+ BMC vs. CABG alone	5.8×10^6	EF +9.7 ± 8.8% (BMC) EDV −11.1 ± 38.6 (BMC)	Echocardiography	
Patel (95) (C)	20	n.a.	CD34+ BMC vs. CABG alone	22×10^6	EF +16.7 ± 3.2% (BMC) EDV −22.0 ± 27.6 (BMC)	Echocardiography	
Hendrikx (108) (R)	20	31.0 ± 23.2 weeks	BMC-MN vs. CABG alone	$60.25 \pm 31.35 \times 10^6$	EF + 6.1 ± 8.6% (BMC-MN)	MRI	
Ahmadi (93) (C)	27	10.5 ± 0.2 weeks	CD133+ BMC vs. CABG alone	$1.89 \pm 0.03 \times 10^6$	EF +3.7 ± 6.3% (BMC)	Echocardiography	
Meta-Analyses of Stem Cell Therapy in Acute Myocardial Infarction							
Hristov (90) (M)	241	~ 7 days	BMC	2.617×10^6	EF +4%	LVA	p = 0.04
Lipinski (8) (M)	698	~5 days	BMC, pred.	531×10^6	EF +3%	LVA, SPECT, MRI	p < 0.001
					Infarct size −6%	LVA, SPECT, MRI	p < 0.001
					ESV −7 ml	LVA, SPECT, MRI	p = 0.002
					EDV −5 ml	LVA, SPECT, MRI	NS
Abdel-Latif (91) (M)	999	~10 days	BMC, pred.	80×10^6	EF +4%	LVA, SPECT, MRI	p < 0.001
					Infarct size −7%	LVA, SPECT, MRI	p = 0.003
					ESV −6 ml	LVA, SPECT, MRI	p = 0.006
					EDV −3 ml	LVA, SPECT, MRI	NS
Burt (92) (M)	1,002		BMC, pred.	n.a.	EF +2% to +5%	Echocardiography, MRI	NS

CABG = coronary artery bypass graft surgery; EDV = end-diastolic volume; LVA = left ventricular angiography; MN = mononuclear; n.a. = not available; NS = not significant; pred. = predominantly; other abbreviations as in Table 1.

ischemic heart failure are very interesting (69). A recent study reported not only a gain in cardiac function but also a clear improvement in quality of life for patients with chronic ischemic heart disease and refractory angina treated after stand-alone bone marrow stem cell injection through lateral minithoracotomy (69).

Interventional studies using intracoronary or endocardial stem cell application have also been performed in the setting of chronic ischemic heart failure. These studies report an improvement of LVEF to a similar extent as in surgical trials. Furthermore, a significant decrease in infarction size and an improved overall myocardial oxygen uptake have been described (6,96). The largest study, STAR (acute and long-term effects of intracoronary Stem cell Transplantation in 191 patients with chronic heARt failure) heart study, included 391 patients with chronic heart failure (New York Heart Association functional class 3.22 and 3.06, respectively; LVEF ≤35%) (97). Within the wide range of 3 months to 5 years after intracoronary BMC therapy, there was significant improvement in hemodynamics (e.g., LVEF, cardiac index), exercise capacity, oxygen uptake, and left ventricular contractility. Importantly, there was a significant decrease in the long-term mortality of treated patients in comparison to the control group (Fig. 2) (97). Thus, intracoronary BMC therapy improves ventricular performance, quality of life, and survival in patients with chronic heart failure.

Dilated cardiomyopathy. In the last years, few data have been reported on stem cell therapy for dilated cardiomyopathy (DCM) (96,98). This first-in-human study of autologous bone marrow cells in DCM, ABCD (Autologous Bone marrow Cell trial in Dilated cardiomyopathy), investigated 44 patients, and the Düsseldorfer ABCD trial investigated 20 patients (96,98). In both studies, none of the patients had coronary disease (excluded by angiography) or myocarditis (excluded by endomyocardial biopsy). In both trials, cell transplantation was performed by the intracoronary administration route in either coronary artery.

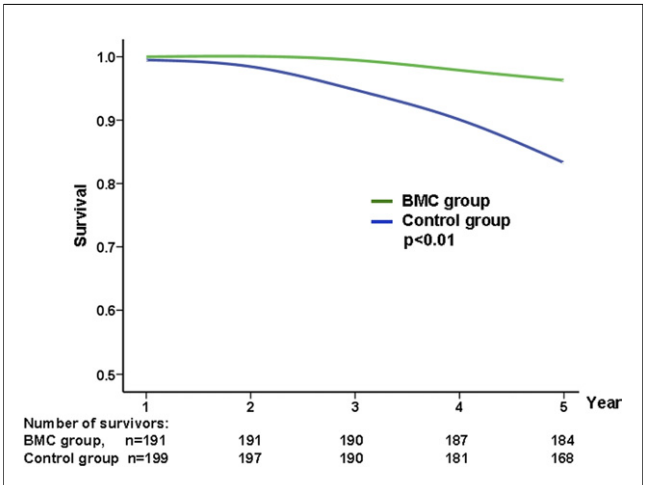

Figure 2 Effect of BMC Therapy on Survival

Effect of bone marrow cell (BMC) therapy **(green line)** on survival of patients with chronic ischemic cardiomyopathy (97). **Blue line** indicates control group.

There was a significant increase in New York Heart Association functional classification. Ejection fraction improved by 5.4% to 8%. Physical ability (functional capacity) rose from 25 to 75 W. Furthermore, reduction of arrhythmias was documented. Both trials found reduction in end-systolic volumes and no change in end-diastolic volumes. These first results show that transplantation of autologous bone marrow cells as well as the intracoronary approach represent a potential effective therapeutic procedure for DCM.

Indications for cell therapy. The therapeutic extract resulting from the 16 largest controlled and randomized studies (n = 1,598) (Table 1) shows for acute myocardial infarction and for chronic ischemic heart failure an improvement of LVEF by a mean 11.3%. Considering the 4 meta-analyses involving 2,940 patients, the increase in ejection fraction (mean 4%) is much lower, but still significant. This hemodynamic pattern is compatible with the symptomatic improvement (New York Heart Association functional class, exercise tolerance) and with reduced mortality in treated patients (Fig. 2).

The best tested indications for BMC therapy are a previous myocardial infarction with large infarct area, aneurysm, and depressed ejection fraction, as well as heart failure due to chronic ischemic heart disease (99). The age of the infarct seems to be less relevant for the regenerative potency of BMCs, because this therapy for old infarcts (>8 years) is almost equally effective as it is for recent infarcts (8 to 14 days). This regenerative phenomenon is probably related to a persistence of the border zone, which is also present in chronic infarcts. Positive results that have also been reported for DCM with severely depressed ejection fraction encourage further studies in advanced heart failure due to heart muscle diseases.

Taking all this into account, it may be concluded that cell transplantation within the first 5 days after acute infarction is not possible for logistical reasons of the critically ill patient and is not advisable because of the inflammatory process (100–102). Although the ideal time point for transplantation remains to be defined, it is most likely between days 7 and 14 after the onset of myocardial infarction.

Clinical Safety

The procedure of intracoronary autologous bone marrow cell transplantation in patients with acute myocardial infarction, chronic coronary artery disease, and nonischemic DCM is effective and safe. No increase of malignant diseases or inadequate progression of coronary artery diseases has been documented (91). To assess any inflammatory response and myocardial reaction after intracoronary autologous stem cell transplantation, white blood cell count, serum levels of C-reactive protein and of creatine phosphokinase are measured before, during, and after treatment, and these data collected revealed no evidence of inflammation. Neither procedural or cell-induced complications nor any other type of side effects have occurred so far.

Ongoing Clinical Trials

Several trials running currently are trying to answer the questions mentioned in the preceding text. Regarding the effect of intracoronary bone marrow progenitor cell infusion in the setting of acute myocardial infarction, placebo-controlled Phase II/III trials like REGEN-AMI (Bone Marrow Derived Adult Stem Cells for Acute Anterior Myocardial Infarction) are of interest. In the field of surgical cell therapy, the recently launched PERFECT (intramyocardial transPlantation of bonE maRrow stem cells For improvEment of post-inFarct myoCardial regeneraTion in addition to CABG surgery) study is the first placebo-controlled, double-blinded, multicenter Phase III trial investigating the effects of intramyocardial BMC injection combined with CABG surgery. Although representing Phase I and II levels, PROMETHEUS (Prospective Randomized Study of Mesenchymal Stem Cell Therapy in Patients Undergoing Cardiac Surgery) is highly interesting because it represents the first-in-human study analyzing the safety and efficacy of intramyocardial injection of mesenchymal stem cells during CABG in patients scheduled for coronary surgery due to ischemic heart disease, as an alternative cell population to the hematopoietic progenitor cell populations mainly used in clinical trials for cardiac regeneration so far. In this respect, the combination treatment of purified endothelial progenitor cells and mesenchymal stem cells has been addressed successfully in a Phase I trial with intramyocardial injection (103). There are several more interesting trials currently recruiting patients, and results from all of these are needed for a valid evaluation of the gain in cardiac function related to stem cell therapy.

Dose-dependent contribution for cardiac recovery. Iwasaki et al. (104) found dose-dependent augmentation of cardiomyogenesis and vasculogenesis after transplantation of human $CD34^+$ cells into rat infarcted myocardium. Enhanced capillary density, inhibition of left ventricular fibrosis, and increased recovery of the left ventricular function was associated with higher numbers of transplanted $CD34^+$ cells. These findings suggest that use of higher doses of $CD34^+$ cells may be more potent for therapeutic application to the damaged myocardium than a lower dose. In their study, they also found that there was no beneficial effect of $CD34^+$ cells in their low-dose group (1×10^3 cells/kg) (104). Recently, clinical data also showed the dose-dependency influence of $CD34^+$ cells on left ventricular function and perfusion (105).

Ethical considerations. The use of human autologous BMCs containing (progenitor) stem cells for cardiac regenerative therapies can be clinically justified and is ethically unquestionable as long as unmodified primary cells are used. No major side effects have been reported so far, especially

with regard to tumor formation. Moreover, in contrast to differentiation of embryonic stem cells to contractile heart cells, there is no arrhythmogenic potential of BMCs, and immunosuppressive therapy is unnecessary. Thus, the therapeutic advantage clearly prevails, and clinical use has already been realized.

Perspectives

Future studies should aim at defining the optimum technique of cell preparation, discovering the best cell type and amount for myocardial regeneration, analyzing their homing characteristics to the cardiac endothelium and to extracardiac organs, improving cell delivery techniques, and trying to establish indications for cell therapy in various heart diseases (62). Joint and cooperative studies between pre-clinical and clinical research are essential. The mechanisms of stem cell-related cardiac repair need to be further investigated and alternative modes of action such as paracrine activity and immunomodulation should be considered. Furthermore, attempts to create dynamic "multi-lineage" cardiac regeneration by combining cell therapy with tissue-engineered scaffolds or cardiac resynchronization therapy (106–108) should be further supported because they offer a realistic perspective to come to an integrated regenerative approach.

As with each new therapy, new questions arise parallel to its clinical use: the following methodologic and therapeutic questions would be worth to be analyzed in the future: 1) to define the optimum technique of cell preparation; 2) to standardize cell separation procedures; 3) to evaluate the quality of the cell end product; 4) to discover the best cell type for myocardial regeneration; 5) to analyze cell homing characteristics to the cardiac niche; 6) to characterize the mode of action of stem cells for cardiac regeneration; 7) to improve cell delivery techniques; and 8) to label stem cells for determining stem cell fate. Interest should be focused on adult stem cell projects that have already proven significant clinical efficacy, but without having any ethical concerns.

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Key Words: cardiac stem cell therapy ■ intracoronary ■ intramyocardial.