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STATE-OF-THE-ART PAPERS

Potential Hazards and Technical Considerations Associated With Myocardial Cell Transplantation Protocols for Ischemic Myocardial Syndrome

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Cell transplantation has recently emerged as a promising therapeutic approach to ischemic cardiomyopathy syndromes. Clinical studies suggest important benefits, including improved myocardial perfusion and function. The safety profile so far seems to be high overall, although the technique may harbor several adverse effects, such as ventricular arrhythmia, acceleration of atherosclerosis or restenosis, and induction of ischemic events. Multiple factors may affect the safety of cell infusion into the diseased heart, including the mode of delivery, the type of cells injected, compound characterization, and the heart status, function, and arrhythmogenic potential. Also, any adjunctive treatment used to enhance cellular homing and/or transdifferentiation increases the likelihood of unexpected local or systemic toxicity or side effects. In the present review, we discuss the potential hazards of this novel treatment and its relationship to technical considerations. (J Am Coll Cardiol 2006;48:1519–26) © 2006 by the American College of Cardiology Foundation

Intramyocardial cell transplantation has recently emerged as a promising therapeutic approach to ischemic cardiomyopathy syndromes. Its goals are to safely reduce cardiac-related symptoms and improve cardiac perfusion and function (1,2). The concept of cell therapy has been examined in animal models and has already been introduced into the clinical arena (3–7). Given the fact that cell therapy, despite multiple small clinical studies, should be considered in its infancy, further investigation should be carefully planned against its potential hazards.

Multiple factors may affect the safety of cell delivery into the diseased heart (Fig. 1): 1) the mode of delivery: intravenous, intracoronary, intramyocardial (percutaneous or direct surgical injection), or retrograde myocardial transvenous; 2) the cell type: bone marrow-derived stem cells (endothelial progenitor cells, hematopoietic stem cells, mesenchymal stromal cells), skeletal myoblasts, or embryonic stem cells; 3) compound characterization: cell dose and volume, rate of injection, and quality control of cellular products; 4) the heart status, function, and arrhythmogenic potential; 5) the time of treatment in relation to the myocardial injury and/or ischemic insult; and 6) the adjunctive treatment used to enhance cellular homing and/or transdifferentiation. In the present review, we discuss the possible risks of this novel treatment and their relationship to technical considerations.

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MODE OF DELIVERY

Intracoronary injection. The use of bone marrow cell implantation was introduced in humans in the wake of findings of myocardial angiogenesis and/or regeneration in several animal models. Its current safety profile and other relevant clinical data are based on limited clinical experience in a small number of patients. No long-term consequences have yet been evaluated (8–10). Furthermore, some patients with acute myocardial infarcts were treated with intracoronary delivery of bone marrow cells at the time of reperfusion of the occluded vessel, even before comprehensive animal data were available (3–7).

In 2004, Vulliet et al. (11) reported that injection of mesenchymal stromal cells into the coronary artery of healthy dogs resulted in augmented myocardial ischemia, as indicated by ST-segment elevation and T-wave changes, as well as frequent ventricular arrhythmia and troponin I elevation. Histopathologic assessment confirmed the presence of microinfarction. Moelker et al. (12) noted similar microinfarctions within the target tissue in a pig model after intracoronary injection of human umbilical cord blood–derived somatic stem cells. In another study, intracoronary delivery of mesenchymal stem cells in pigs was associated with decreased distal blood flow (13). In human studies (3–7), the combined experience from more than 100 patients with recent myocardial infarction suggested that transplantation of bone-marrow-derived adult progenitor cells by intracoronary infusion was both feasible and safe. There was no excessive myocardial damage (e.g., repeated elevation of troponin) or adverse systemic inflammatory response related to the injection (e.g., elevation of C-reactive protein), and there were no deaths, malignant

Abbreviations and Acronyms

G-CSF = granulocyte colony-stimulating factor
GM-CSF = granulocyte-macrophage colony-stimulating factor
VEGF = vascular endothelial growth factor

arrhythmias, or arrhythmias induced by electrophysiological studies during the post-discharge follow-up (range 3 to 12 months). However, in a pilot study of 6 patients with ischemic cardiomyopathy who received intracoronary infusion of mononuclear autologous bone marrow cells, 1 patient acquired hypotension with troponin elevation, probably because of microembolization of the cellular compound (14).

Interestingly, Kang et al. (15) noted excessive restenosis rates after the intracoronary infusion of peripheral blood–derived mononuclear cells enriched by granulocyte–colony-stimulating factor (G-CSF) in a small group of patients with recent myocardial infarction treated with angioplasty of the infarct-related artery (15). Similarly, in another clinical trial (16), infusion of a selected subpopulation of bone marrow CD133+ cells into the infarct-related artery was associated with significant in-stent restenosis at the 4-month follow-up in 7 of 19 patients. Two patients showed complete reocclusion, and 2 acquired new lesions in the infarct-related artery. This rate was significantly greater than the rate in patients treated with placebo. Furthermore, Mansour et al. (17) recently reported that intracoronary administration of hematopoietic bone marrow stem cells seemed to be associated with accelerated progression of distal atherosclerosis in the infarct-related artery. Other studies, however, showed no relationship between intracoronary injection and increased rate of restenosis or accelerated atherosclerosis (5), or between G-CSF administration and restenosis (18,19). This discrepancy is exacerbated by the absence of reassuring animal data and the emerging safety controversy concerning cellular and cytokine compounds (for more details, see the section on Adjunctive Treatment), and it underscores the need for planning appropriate safety end points. Additional red flags were raised by Schachinger et al. (4) in their 1-year follow-up study, in which 2 patients (3.4%) treated for myocardial infarction by intracoronary cell injection sustained stent thrombosis. It remains unclear whether this complication was related to the repeated low-pressure balloon inflations performed at the site of the previously implanted stent, at a time when stent endothelialization was still minimal and fragile. If confirmed in larger studies, a change in injection technique may be necessary to avoid further intracoronary endothelial damage.

The recent discovery that circulatory cells are capable of differentiating into vascular structures (20) highlights the need for angiographic follow-up of patients treated with progenitor stem-cell infusions. In addition, researchers have found that angiogenesis and inflammation play an important role in atherosclerotic plaque formation and that lesion expansion and may accelerate the coronary atherosclerosis that occurs after infusion of progenitor cells (21).

These studies underscore the cautious approach necessary to the use of intracoronary stem-cell infusion in humans. Safety assessments in humans must account for the small diameters of the bone marrow and progenitor cells used in clinical studies (10 to 12 μm) compared with the mesenchymal stromal cells or umbilical cord blood–derived somatic stem cells (20 μm) that caused microinfarctions in animals (11–13). Also, freshly aspirated cells are smaller than processed cells (11). In addition, parameters such as cell dose and concentration, compound viscosity, and rate of coronary infusion may have important impacts on the safety of the treated myocardium, as may the status of the recipient tissue, because ischemic myocardium may differ in microresponses and/or macroresponses from infracted myocardium. Thus, clinical research needs to be carefully planned with selection of the appropriate delivery method as well as cell population and dosing parameters that may carry the best risk-to-benefit profile.

Intramyocardial injection. Intramyocardial delivery of therapeutic substances can be achieved by either direct injection after open-chest thoracotomy (transepicardial) or catheter-based techniques (transendocardial) using electromechanical mapping or fluoroscope guidance (22). Our group previously examined the safety of the electromechanically guided injection catheter system in porcine hearts (23,24). There were no cases of sustained arrhythmia, and no gross evidence of cardiac perforation, peripheral embolization, or stroke. However, in some of the injection sites, the endocardial injury seemed to be exaggerated. These injuries could be classified into 3 types: 1) type A injury included the desired formation of endomyocardial slots combined with microscopic tracks of hemorrhagic infiltration surrounded by the injected compound (Figs. 2A and 2B); 2) type B injury induced the formation of endocardial ecchy-

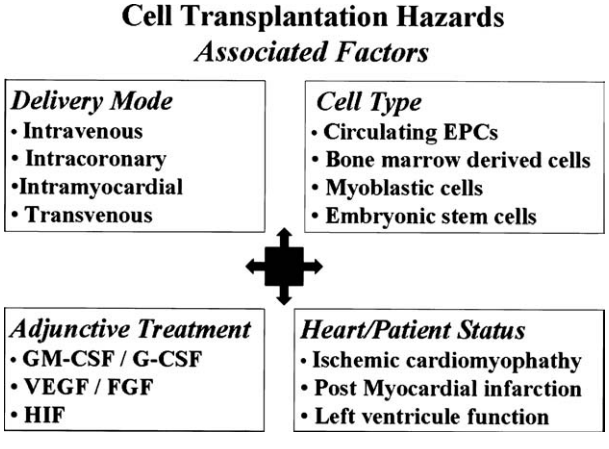

Figure 1. Factors influencing cell therapy. EPCs = endothelial progenitor cells; FGF = fibroblast growth factor; G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor; HIF = hypoxia inducible factor; VEGF = vascular endothelial growth factor.

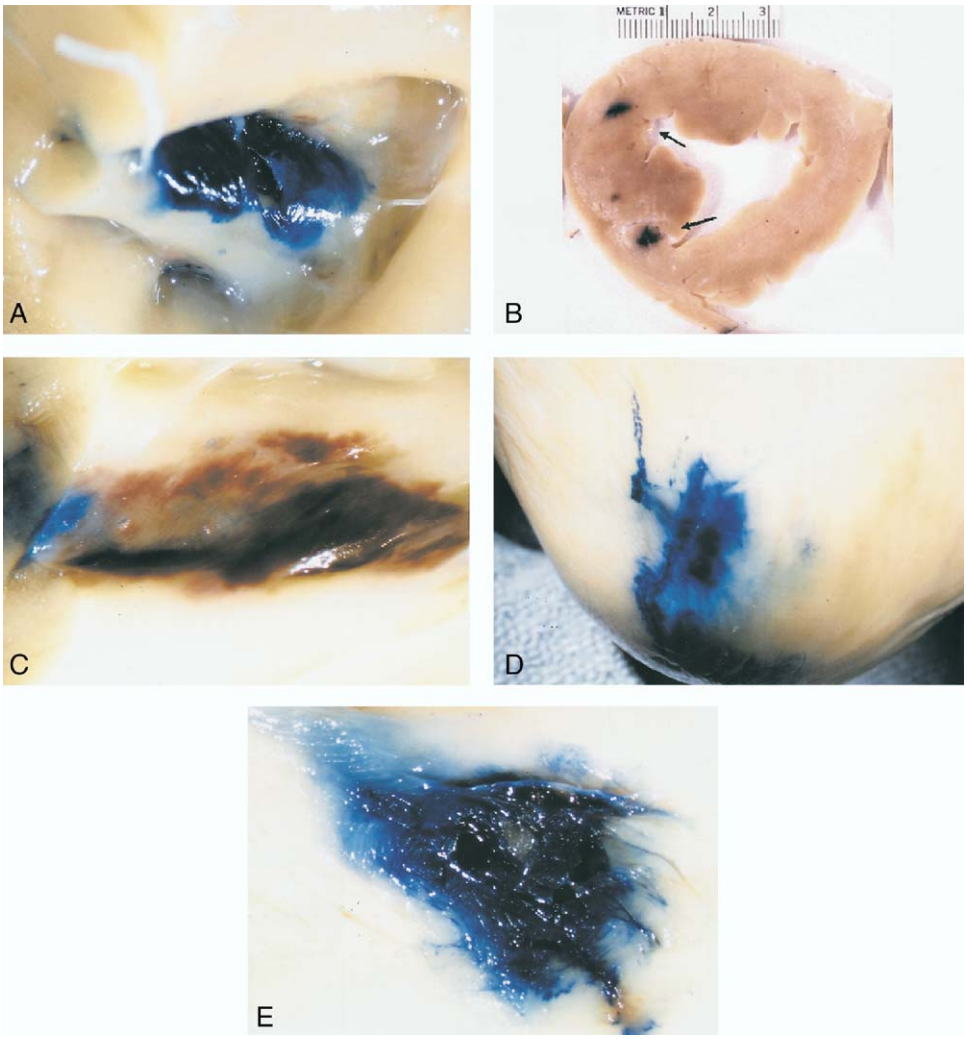

Figure 2. **(A)** Endomyocardium showing spread of injected methylene blue dye. **(B)** Gross pathology of cross-sectioned hearts injected with methylene-blue dye tracer. **(C)** Endocardial ecchymosis resulting from intramyocardial injection of methylene blue. **(D and E)** Epicardial staining with methylene blue.

mosis caused by an exaggerated or forceful injection (Fig. 2C); 3) type C was a transmyocardial injury with possible deterioration to myocardial perforation and pericardial tamponade, also related to an excessive injected volume (Figs. 2D and 2E). Similar to our findings, other data derived from animal (25) and human (26–28) studies indicated no arrhythmia, infection, myocardial inflammation, increased fibrosis, or perforation caused by catheter-based techniques (24). In addition, in a report by Dohmann et al. (29) on the postmortem findings on a single patient after transendocardial injection of bone-marrow-derived mononuclear cells, there was no abnormal or disorganized tissue growth, no abnormal vascular growth, and no enhanced inflammatory reaction in the heart.

By contrast, Kastrup et al. (30) reported direct injury from intramyocardial injection of vascular endothelial growth factor (VEGF) in 5 patients (6.25%) with severe stable angina who participated in the Euroinject One study. Complications included pericardial tamponade, high-degree atrioventricular block, ST-segment elevation, myocardial infarction, embolic events, and sepsis, all of which were procedure related and independent of the injected compound. These findings emphasize the importance of technical considerations, especially in infrequently used procedures, and they may be minimized by careful patient selection and preprocedural assessment by different imaging modalities. Detailed patient notification of the potential procedure-related risks is mandatory.

Regardless of the delivery method, the local effects of the transplanted cells must be thoroughly considered. These include exaggerated inflammation or aberrant tissue formation that might impair myocardial function. Yoon et al. (31) showed that direct transplantation of unselected bone marrow cells into the acutely infracted myocardium of murine hearts may induce significant myocardial calcification in both infarcted and normal myocardial regions. Similarly, transplanted undifferentiated mesenchymal stem cells have been shown to develop into fibroblastic scar tissue (9). Li et al. (32) did not find calcification after injection of bone marrow cells in dogs, although there were fibrotic changes

within the myocardium that could have been cell- or injection-related. Stamm et al. (33) treated 6 patients after recent (<3 months) myocardial infarction with bone-marrow-derived CD133+ cells during coronary artery bypass surgery. Supraventricular arrhythmia developed in 2 patients, and pericardial effusion developed in 2 patients. However, the lack of a control group and the small number of patients precluded a definitive conclusion regarding a cause-and-effect relationship. Other studies (34–36) of local stem cell transplantation during open-heart surgery reported an absence of clinically relevant inflammatory responses or myocardial damage or aberrant tissue formation. We recently studied 27 patients with refractory myocardial ischemia who underwent transendocardial injection of autologous unfractionated bone marrow cells (37). The 1-year survival rate was 100%, although 7 patients (26%) required an additional revascularization procedure (angioplasty or bypass surgery). Interestingly, in 5 of these patients, the intervention was performed in a vessel supply remote from the injected territory because of late restenosis and disease progression. Again, as no control group was used, we could not determine whether these processes were accelerated by the cell injection or were part of the natural history of the underlying disease. Nevertheless, this observation underscores the potential need for angiographic follow-up of patients undergoing experimental cellular transplantation protocols to exclude accelerated coronary atherosclerosis and late restenosis.

Heart arrhythmic potential. Most of the candidates for experimental stem cell strategies are patients with heart failure, previous myocardial infarction, and severe myocardial ischemia, and all are at considerable risk of arrhythmia and sudden cardiac death.

However, studies of intramyocardial skeletal myoblast injection during coronary bypass surgery or by catheter-based technique in patients with depressed ischemic cardiomyopathy have shown a high incidence of serious ventricular arrhythmia (Table 1), whereas studies using bone-marrow-derived cells did not (Table 2). Menasche et al. (38) reported on 10 patients with a severely reduced ejection fraction who underwent coronary artery bypass grafting and myoblast injection into scar myocardial tissue that was supplied by a totally occluded vessel and could not receive a surgical graft. Four patients had sustained ventricular tachycardia at 11 to 22 days after the procedure, of whom 2 had additional episodes of ventricular arrhythmias 5 and 9 months later. All 4 patients required an implantable defibrillator. Smits et al. (39) treated 5 patients with severe heart failure caused by anterior myocardial infarction with transendocardial injection of myoblasts as the sole procedure. One patient had ventricular tachycardia 6 weeks later and required an implantable defibrillator, and 8 patients had 2 episodes of sudden death and 3 events of ventricular tachycardia. In another study, episodes of ventricular tachycardia were observed in 1 of 9 patients with ischemia-driven heart failure treated by retrograde transcoronary venous myoblast injection (40). Collectively, these studies suggest an arrhythmogenic potential of direct myocardial injection of myoblasts into scar tissue irrespective of the delivery technique. An alternative suggestion was made by Chachques et al. (41), who noted no serious arrhythmias in 20 patients over a mean follow-up period of 14 months after injection of myoblasts expended in an autologous medium rather than fetal bovine serum. This technique was based on the assumption that trace contamination with xenogeneic proteins can provoke arrhythmias because of an immune (i.e., rejection-type) reaction at the injection site. Fuchs et al. (37) found that the injection of bone marrow–derived cells was safe in patients with preserved left ventricular function. In another study in 14 patients with severely reduced left ventricular function caused by ischemic cardiomyopathy, the injection of bone marrow–derived mononuclear cells did not induce early arrhythmia, but 1 patient suffered sudden cardiac death 14 weeks after treatment (27).

Table 1. Incidence of Serious Ventricular Arrhythmias With Intramyocardial Transplantation of Skeletal Myoblasts

Study	Patients (n)	Procedure/ Target Tissue*	Revascularization of Injected Segments	Mode of Injection	No. of Cells (Mean × 10^6)	Follow-Up (Months)	Serious Ventricular Arrhythmia (n)	SCD (n)
Menasche et al. (38)	10	CABG EF <35% Scar	No	Transepicardial	871	10.9	4 (40%)	0
Smits et al. (39)	5	EF 20%–45% Scar	No	Transendocardial	296	6	1 (20%)	0
Smits et al. (39)	8	NA	No	Transendocardial	NA	3	3 (37.5%)	2 (25%)
Siminiak et al. (40)	9	EF 25%–45% Scar	No	Transcoronary-venous	57	6	1 (11.1%)	0
Chachques et al. (41)	20	CABG EF 28% Scar, peri-scar	Yes	Transepicardial	300	14	0	0
Herreros et al. (71)	12	CABG EF 35% Scar, peri-scar	Yes	Transepicardial	211	3	0	0

*Patient population refers to the global function of myocardium and performance of cell transplant concomitant with CABG. Scar or peri-scar refers to the injection site.
CABG = coronary artery bypass grafting; EF = ejection fraction; NA = not available; SCD = sudden cardiac death.

Table 2. Incidence of Serious Ventricular Arrhythmia With Myocardial Cell Transplantation of Bone Marrow Cells or Circulating-Blood-Derived Progenitor Cells

Study	Patients (n)	Procedure or Event/Target Tissue*	Revascularization of Injected Segments	Cell Type and Mode of Injection	No. of Cells (Mean × 10^6)	Follow-Up (Months)	Serious Ventricular Arrhythmia (n)	SCD (n)
Refs. (3–7,15)	113	Acute MI	Yes	BMMNC, CPC Intracoronary	1.5–33.6	3–12	0	0
Perinet et al. (27)	14	Ischemic EF <40%	No	BMMNC Transendocardial	25.5	4	0	1 (7.1%)
Silva et al. (28)	5	Ischemic EF <40%	No	BMMNC Transendocardial	NA	6	0	0
Fuchs et al. (37)	27	Ischemic EF >30%	No	BMMNC Transendocardial	28	12	0	0
Stamm et al. (33)	6	CABG Peri-scar	No	BMC (AC133+) Transepicardial	1.5	9–16	0	0
Ozbaran et al. (34)	6	CABG EF <25% Ischemic	Yes	CPC (CD34+) Transepicardial	32.6	4–10	0	0
Galinanes et al. (35)	14	CABG Scar	Yes	BMC CD34/117 Transepicardial	31.5	10	0	0
Archundia et al. (36)	5	CABG Scar, peri-scar	Yes	CPC CD34+ Transepicardial	20	7	0	0

*Patient population refers to the global function of myocardium and performance of cell transplant concomitant with treatment of acute MI, ischemic myocardium, or CABG. Scar or peri-scar refers to the injection site.

BMC = bone marrow cells; BMMNC = bone marrow mononuclear cells; CABG = coronary artery bypass grafting; CPC = circulating-blood-derived progenitor cells; EF = ejection fraction; MI = myocardial infarction; SCD = sudden cardiac death.

Thus, malignant arrhythmias are apparently more likely to occur after myoblast transplantation than after bone marrow cell injection, especially when the cells are injected directly into nonviable (scar) tissue. It is conceivable that lack of gap junction formation between the myoblasts and cardiomyocytes may serve as a substrate for the formation of a re-entry cycle and resultant ventricular arrhythmia (42). Fouts et al. (43) recently reported that skeletal myoblasts injected into the scar of a myocardial infarction do not significantly alter impulse propagation (which is already altered by the scar tissue) or induce greater arrhythmia compared with the myocardial infarction alone. However, in viable myocardium, skeletal myoblasts can affect impulse propagation through pacing from the epicardium, not the endocardium. This difference, according to their study, did not translate into an increase in arrhythmia events. Alternatively, the injected cells themselves, or the local injury/edema induced by the intramyocardial injection itself, may cause arrhythmia in already highly susceptible patients. Zhang et al. (44) explored the arrhythmogenic potential of cardiomyocytes derived from pluripotent embryonic stem cells and embryonal carcinoma cells. The electrical recordings showed that both cell lines manifested spontaneous activity, low dV/dt, prolonged action potential duration, and easily triggered arrhythmias. These findings raise concerns about the use of stem cells for transplantation therapy because they may act as an arrhythmogenic source via any of the 3 classic mechanisms: re-entry, automaticity, or triggered activity.

In conclusion, current data suggest that the risk of arrhythmia occurring after myocardial cell transplantation may be increased by several factors: 1) the type of cell injected; 2) the local myocardial milieu and electrical properties of the recipient tissue; 3) the presence of global and regional left ventricular function; 4) the ex vivo cell-expansion technique; and 5) the timing of the transplantation relative to the ischemic or infarction events.

Unregulated differentiation. Bone marrow is a multicellular tissue composed of hematopoietic precursors, their differentiated progeny, and a stromal cell network. The stroma contains a heterogeneous mixture of mesenchymal stem cells, multipotent adult progenitor cells, adipocytes, reticulocytes, endothelial cells, fibroblasts cells, and osteoblasts, which can differentiate into a variety of nonhematopoietic lineages (45–47). Because the molecular signaling, underlying mechanisms, temporal parameters, and local conditions that control cellular differentiation are still currently obscure, the potential of uncontrolled differentiation of the injected cells is a major concern. For example, embryonic stem cell transplantation has been associated with teratoma formation (48), and the cells were found to show chromosomal abnormalities (49). Others noted a possible association of high levels of circulating endothelial progenitor cells and the risk of certain cancers, such as multiple myeloma (50), which might be caused by angiogenic effects (51). However, as of today, no clinical studies have suggested the formation of aberrant tissue, enhancement of scar formation, or induction of tumor growth.

ADJUNCTIVE TREATMENT

The systemic administration of cytokines to accelerate cell mobilization, homing, and/or transdifferentiation has been tested in many preclinical and clinical studies (52–54). This technique is potentially hazardous because of the cytokine's multisystemic effects. Specifically, it is known to exert a variety

of prothrombotic effects on both coagulation proteins and platelets (55,56). The administration of granulocyte–macrophage colony-stimulating factor (GM-CSF) in a rat model was found to facilitate infarct expansion and left ventricular remodeling (57), and in humans, sporadic cases of myocardial infarction were reported in cancer patients and in healthy subjects receiving G-CSF (58–63). The G-CSF also increased levels of C-reactive protein in healthy subjects (64) and caused cardiac ischemia and infarction in patients with severe coronary disease (65).

The safety of G-CSF and GM-CSF administration as an adjunct to cell injection has been examined (Table 3), although the findings are still controversial. Kang et al. (15) reported that G-CSF administration with or without mononuclear cell injection aggravated in-stent restenosis in 7 of 10 patients after acute myocardial infarction treated by stent-based angioplasty. Boyle et al. (66) described a patient in whom acute coronary syndrome developed 2 months after G-CSF mobilization of CD34+ cells. Others, however, found no association of G-CSF administration and restenosis in patients with acute myocardial infarction who underwent successful percutaneous intervention (18,19,67). The high rate of in-stent restenosis reported by Kang et al. (15) compared with the other studies (18,19,67) could result from different patient populations (non–ST-segment elevation myocardial infarction vs. ST-segment elevation myocardial infarction) with different sequence protocols (G-CSF treatment before or after coronary intervention).

An additional concern is that G-CSF, because of its thrombogenic and inflammatory properties, may accelerate plaque instability and coronary thrombogenicity. Powell et al. (68) reported that G-CSF administration in 16 patients with severe coronary artery disease mobilized hematopoietic progenitor cells into circulation without adverse effects. However, 2 of the patients with advanced disease and recurrent ischemia experienced serious adverse events, namely, non–ST-segment elevation and myocardial infarction at 8 h after the fifth G-CSF dose, and fatal myocardial infarction 17 days after treatment (69). In another study, G-CSF administration improved physical performance in 16 patients with chronic heart failure, but a subgroup of patients with ischemic cardiomyopathy had cardiac side effects, including episodes of dyspnea or angina that occasionally coincided with particularly high leukocyte counts; there was 1 episode of fatal ventricular fibrillation (70). Thus, the overall safety profile of G-CSF, especially in patients with coronary disease, is of concern, and its efficacy is questionable at best.

Quality control of cellular products. Most cellular compounds used today are autologous, although some studies of allogenic cells have recently been initiated. Although allogenic cell compounds must be prepared under stringent laboratory conditions, autologous cell preparation is not standardized, especially when the cells are to be injected soon after harvesting. Moreover, the angiogenic potential of autologous cell compounds is not routinely evaluated before

Table 3. Hazards of G-CSF Stimulation

Study	Patients (n)	Event	Revascularization	Adjunctive Treatment	Cell Dose	Follow-Up (Months)	In-Stent Restenosis (n)	ACS/MI (n)	Serious Ventricular Arrhythmia (n)	Cardiac Death (n)
Kang et al. (15)	10	Acute MI	PCI	No/Intra-coronary CD34+*	10 μg/kg 4 days	6	7 (70%)	0	0	0
Zohlnhofer et al. (19)	56	Acute MI	PCI	No	10 μg/kg 5 days	4–6	19 (35.2%)†	0	1 (1.8%)	1 (1.8)
Ince et al. (18)	25	Acute MI	PCI	No	10 μg/kg 6 days	6	4 (16%)†	0	0	0
Valgimigli et al. (67)	10	Acute MI	PCI	No	5 μg/kg 4 days	6	0	0	0	0
Nienaber et al. (72)	50	Acute MI	PCI	No	10 μg/kg 6 days	4	NA	0	0	0
Boyle et al. (66)	5	Ischemia EF >25%	PCI	Intra-coronary CD34+	10 μg/kg 4 days	12	0	1 (20%)	0	0
Archundia et al. (36)	5	Ischemia	CABG	Transepicardial CD34+	300 mg 5 days	7	0	0	0	0
Hill et al. (69)	16	Ischemia	No	No	10 μg/kg 5 days	3	NA	2 (12.5%)	0	1 (6.25%)
Huttmann et al. (70)	16	Chronic heart failure	No	No	Variable for 10 days, 4 courses	27	NA	2 (12.5%)	1 (6.25%)	5 (31.2%)

*Seven patients of the 10 received adjunctive bone marrow cell transplantation; †no significant difference from the control group.
ACS = acute coronary syndrome; CABG = coronary artery bypass grafting; G-CSF = granulocyte colony-stimulating factor; MI = myocardial infarction; NA = not available; PCI = percutaneous coronary intervention; SCD = sudden cardiac death.

their administration, and the only relatively controlled parameter is the number of cells. The percentage of subpopulations of cells also varies, imposing further complexity on cell dosing. Those hurdles complicate the ability to assess the dose-and-effect relationship, a factor of paramount importance in the safety and efficacy of therapeutic compounds (71,72).

Summary. Cell transplantation is a promising therapeutic approach to ischemic cardiomyopathy syndromes. Clinical studies suggest beneficial effects, including improvement of myocardial perfusion and function. The increasing experience with these techniques indicates a high safety profile overall, although they pose several potential dangers, such as ventricular arrhythmia, acceleration of atherosclerosis and restenosis, and induction of ischemic events. It is important to underscore that the general adverse event rate is currently low, and the specific cases reported were strongly related to the type of cell injected, the characteristics of the patient population, and the adjunctive use of cytokines. Optimization of cell therapy requires not only larger clinical trials, but also standardization of cell preparation methods, potency assessment, and controlled administration, which together may allow for a better assessment of the risk benefit.

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