Stem cells in acute myocardial infarction: the good, the bad, and the ugly

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This editorial refers to 'Intracoronary infusion of progenitor cells is not associated with aggravated restenosis development or atherosclerotic disease progression in patients with acute myocardial infarction'† by B. Assmus et al., on page 2989

Any new form of treatment, when based on solid experimental observations, initially generates a lot of enthusiasm among researchers as well as among patients (when media get involved). If the initial positive results in observational studies are then confirmed in small randomized trials with surrogate endpoints and finally in large randomized trials with clinical endpoints, the new treatment gains momentum and becomes common practice when incorporated in guidelines (for instance, the use of ACE inhibitors in patients with heart failure). At the other extreme, if the initial positive results are not confirmed in controlled randomized trials, the new treatment is quickly forgotten (for instance, the use of positive inotropic agents in patients with heart failure). As clinicians, we know, however, that we have to accept the grey area where things can remain uncertain for years or even decades. A good example is offered by lipid-lowering drugs: in spite of compelling evidence in the sixties that hypercholesterolaemia is a key atherogenic stimulus, statins have entered guidelines in the nineties only. The simple reason for this prolonged hovering in the grey area is that lipid-lowering drugs used prior to statins were able to significantly reduce cholesterol levels, but this reduction was not large enough to translate into a significant reduction of clinical endpoints. More recently, growing attention has been paid to the issue of safety. For instance, non-steroidal anti-inflammatory drugs are under close scrutiny because of an increased risk of thrombotic complications which went unnoticed during the last few decades.

The interpretation of the growing number of trials of cell-based therapy following acute myocardial infarction (AMI) has to be considered in this broad context. After the seminal observation in 2001 by Anversa et al.† that the human heart is not a post-mytotic organ, several studies in experimental models have confirmed that bone marrow cells (BMCs) injected locally into the myocardium or mobilized from bone marrow by cytokines could regenerate the infarcted myocardium and improve cardiac function. For its potential to mend broken hearts, a large attention in the public opinion and in the media has driven stem cell research to run, perhaps too soon, from bench to bedside, even after that the initial positive experimental results failed to be confirmed in other studies. In this complex scenario, in which cell-based treatment of AMI is in the grey area, it is possible to identify the good, the bad, and the ugly, as in the old movie directed by Sergio Leone.

The good

Taken together, the results of clinical trials of intracoronary BMC in patients treated with a primary percutaneous coronary intervention (PCI) are encouraging. Early observational studies suggested a significant favourable effect on left ventricular function. The results of randomized studies are more controversial. The BOOST trial showed an improvement in the left ventricular ejection fraction (LVEF) at 6 months in patients randomized to intracoronary BMC, compared with controls, but without a significant difference at 18 months. In another study, Janssens et al. failed to find an improvement in the LVEF, although they observed a significant reduction of infarct size. The recently published ASTAMI trial failed to find a significant improvement in the LVEF assessed by cardiac magnetic resonance, single photon emission tomography, and echocardiography. In contrast, in the REPAIR-AMI trial, Schachinger et al. reported a significant increase of LVEF at ventricular angiography; intriguingly, BMC-treated patients exhibited a significantly lower rate of pre-specified major cardiovascular events (including death, recurrence of myocardial infarction, and any revascularization procedure), although the study was not powered to test differences in clinical endpoints. Lack of consistent effects of BMC on left ventricular function in these early randomized trials is probably related to their limited statistical power and to differences in enrolment criteria, BMC processing, timing of BMC injection, and methods used to assess cardiac function. It is worth noting that the beneficial effects observed in some of these trials are probably related to paracrine effects of BMC favourably influencing neovascularization effects of BMC favourably influencing neovascularization.
and apoptosis, whereas a convincing demonstration of therapeutic myocardial regeneration in humans is still lacking.\(^2\)

**The bad**

Two recent studies have raised concern with respect to the safety of BMC after AMI, an important issue for a form of treatment so far associated to mild and non-reproducible beneficial effects on surrogate endpoints. In one study, Kang et al.\(^7\) found in-stent restenosis in five of seven patients treated with granulocyte colony stimulating factor (G-CSF) for 5 days, followed by bare metal stent implantation and by intracoronary BMC infuision; notably, they found a correlation between late loss and improvement in the LVEF at follow-up. In addition, in a non-randomized study in 38 patients, Mansour et al.\(^8\) found that the infusion of CD133\(^+\)-enriched BMC was associated with greater in-stent proliferation and larger luminal loss in non-stented distal segments of the infarct-related artery, which resulted in a significant decrease in coronary flow reserve. Thus, the report of Assmus et al.\(^9\) in this issue of the Journal, showing that intracoronary infusion of BMC did not aggravate restenosis development nor was associated with an increase of cardiovascular events, including the necessity for repeated coronary revascularization procedures, is very reassuring. Indeed, this is the largest cohort of patients so far reported. Obviously, a major limitation of this study is its retrospective design in which patients treated with intracoronary BMC were compared with a matched, historical patient population. Thus, it is impossible to exclude that confounders might have masked potential detrimental effects of intra-coronary BMC. The authors did their best, nevertheless, to adjust for confounders with an appropriate multivariable analysis, which identified diabetes and acute gain, but not BMC administration, as independent predictors of restenosis.

The risk of accelerated atherosclerosis associated to intracoronary administration of BMC observed in the studies by Kang et al.\(^7\) and Mansour et al.\(^8\) might be due to the prevalence of pro-inflammatory stimuli caused by co-administration of cytokines or by BMC manipulation. Interestingly, in a more recent study, Kang et al.\(^10\) found an improvement in the LVEF in the absence of a higher rate of in-stent restenosis in post-AMI patients successfully revascularized by drug-eluting stent (DES) implantation, who received G-CSF, followed by intracoronary BMC infusion. In this study, the anti-inflammatory effect of DES was probably sufficient to counterbalance the potential pro-inflammatory action of G-CSF.

Taken together, these findings suggest that the risk of accelerated atherosclerosis has to be taken into account in the cell-based treatment of AMI, but this potential risk is protocol-dependent and is not a direct consequence of intracoronary BMC administration.

**The ugly**

Thus, the good is emerging in the form of some improvement in the left ventricular function associated to the cell-based therapy of AMI, and the bad is the potential, but evitable, risk of accelerated atherosclerosis. What about the ugly?

The ugly might take the form of an uncontrolled proliferation of small trials of cell-based treatment of AMI that might weaken the wave of interest in this new form of treatment, should they produce inconsistent results. This risk has recently been highlighted by the "Task force of the European Society of Cardiology concerning the clinical investigation of the use of autologous adult stem cells for repair of the heart".\(^11\)

In order to avoid that the ugly enter the scene, it is important that groups that have interest and experience in this exciting field put together their efforts in order to design large prospective randomized trials with clinical endpoints. These trials should valorize the information deriving from clinical more than from experimental observations, as the human model is peculiar: patients are much less homogeneous than animals. The probability of a clinically relevant success of well-designed trials is high, as predicted by the reproducible observation that patients who, spontaneously, are 'good mobilizers' of BMC after AMI do remarkably better with regard to left ventricular remodelling than 'poor mobilizers'.\(^12,13\) In order to fully exploit the potential of cell-based therapy of AMI, two issues are critical: (i) inclusion criteria; (ii) BMC function and homing. With regard to the first issue, patients who have the highest probability of beneficial effects are poor mobilizers of BMC with a low LVEF. With regard to the second issue, the BMC function is known to be depressed in patients with coronary risk factors. Yet, there are ways to improve it, including co-administration of statins and/or mobilizing factors (such as erythropoietin, a cytokine with low pro-inflammatory profile).\(^2\) Finally, BMC homing is probably denied by the 'no-reflow' phenomenon which might be limited by co-administration of microvascular vasodilators.\(^14\)

In summary, after the promising results of initial observational studies and of randomized trials with surrogate endpoints, cell-based treatment of AMI will leave the grey zone only if large randomized trials will reproducibly and convincingly show that this innovative form of treatment can reduce the rate of major cardiac events in the absence of accelerated atherosclerosis. To reach this ambitious goal, it is important to abandon the formula 'one size fits all', frequently utilized in drug-based clinical trials, by infusing efficient BMC into a coronary circulation patent enough to allow their homing into a myocardium which really needs this innovative form of treatment.

**Conflict of interest**: none declared.

**References**


Clinical vignette

Cardiac lymphangioma: a benign cardiac tumour

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A 21-year-old woman without past medical history was referred to our intensive care unit for a first episode of sustained palpitations, but she reported some short lasting episodes during the last 9 months. Electrocardiogram registers a regular rapid (220 bpm) wide QRS complexes tachycardia. The ventricular origin of the tachycardia was confirmed by electrophysiological study.

A large tumoural mass (10 × 12 cm) included in the posterolateral wall of the left ventricle was visualized by trans-thoracic echocardiogram (Panel A). The echogenic signal of the tumour was identical to the normal myocardium and there was no limit between tumour and normal myocardium. In order to specify the topography of the tumour and its relationship with adjacent organs, magnetic resonance imaging (Panel B) focused on the thoracic area was performed and the echocardiographic findings confirmed.

Percutaneous myocardial catheter biopsy allows an histological examination of the tumour (Panel C), which demonstrated a cardiac lymphangioma. This benign neoplasm is characterized by endothelial-lined, thin-walled spaces that contain lymph (Panel C-arrow 1) and disjoint native myocytes (Panel C-arrow 2). It constitutes an exceptional form of cardiac tumour (only six cases published) mainly discovered during childhood.

Given the extension of the tumour within the myocardium, a surgical resection was impossible. A cardioverter defibrillator was implanted to prevent sudden death. She had some recurrences of ventricular tachycardia converted to sinus rhythm by the device and continue to do well after a follow-up of 18 months. A heart transplant is envisioned.