It has now been more than a decade since clinical scientists began to explore a potential beneficial effect of administering cells to the ischemically injured heart. Stimulated by pioneering experimental studies that showed that bone marrow–derived cells (BMCs) might regenerate infarcted myocardium, clinicians quickly translated this concept into clinical application. Although it was prudent for the initial clinical application to use mononuclear BMCs, on the basis of more than 20 years of experience with these cells by our colleagues in hematology for reconstitution of bone marrow, with demonstrated excellent safety with respect to adverse cardiovascular effects (which is of paramount importance), it became obvious during subsequent experimental studies that the capacity of these cells to form cardiomyocytes by transdifferentiation was very limited. Nevertheless, despite the lack of significant transdifferentiation of the applied cells to cardiomyocytes, the contractile function of experimentally infarcted hearts improved to a significant extent. These insights advanced the concept that BMCs administered to the heart release soluble factors that mediate cardiac repair, neovascularization, and cytoprotection. Indeed, more recent studies supported this paracrine hypothesis by demonstrating that bone marrow–derived c-Kit+ cells stimulated endogenous cardiogenic progenitor activity and new cardiomyocyte formation even in the absence of transdifferentiation of the administered BMCs. Likewise, increased capillary density and improved blood flow recovery after ischemia are well established to occur after BMC administration into ischemic animal models, although very few of the transplanted cells are incorporated into the vasculature. Finally, in an attempt to decipher the functional relevance of the cell fate of administered BMCs, Yoon et al infected cells with inducible suicide genes under the control of cardiovascular cell–specific promoters, thus enabling the selective depletion of the individual cell lineage acquired by the administered undifferentiated BMCs. The observation that elimination of endothelium- and vascular smooth muscle–committed but not cardiac-committed cells was associated with an abrogation of improved contractile recovery after myocardial infarction indicated that BMC administration preferentially targeted the vasculature, and improved cardiac function may be secondary to enhanced perfusion and microvascular function. Indeed, it was shown 25 years ago that an inadequate adaptation of the capillary vasculature is the major determinant of the compensatory reserve capacity of the infarcted heart.

Although these experimental studies have significantly enhanced our understanding of the potential mechanisms underlying a beneficial effect of BMC administration in acutely ischemic hearts, the clinical trials running in parallel during the last decade have provided rather heterogeneous results thus far. Although all clinical trials reported the remarkable safety of intracoronary administration of BMCs in patients with acute myocardial infarction, the overall effect on improvement in ejection fraction has been modest and significantly less persuasive than the expectations raised by the results with preclinical animal models. What could be the reasons for these discrepancies? First, the use of autologous BMCs for clinical application may affect the potency of the cellular product, because it is well known that age and risk factors for coronary artery disease impair both the functional capacity and the paracrine activity of isolated BMCs. Second, efficient cell therapy requires recruitment and retention of the applied cells into the targeted region of the heart. Indeed, recent data demonstrate a direct relationship between the number of cells retained acutely and the recovery of cardiac function after ischemia in animal models. Cell isolation procedures and storage conditions interfere majorly with the signaling mechanisms responsible for recruitment of BMCs after infusion into the infarct-related artery, the current method of choice for cell administration in patients with acute myocardial infarction. Timing of BMC administration after acute ischemic injury may compromise cell retention by altering the signals that emanate from the niche in the peri-infarct target region of the heart. Finally, microvascular obstruction may even prevent access of the intra-arterially administered BMCs to the infarct region and thus limit recruitment of the cells. All of these mechanisms likely contribute to the heterogeneous results of different clinical trials using different cell preparation methods, different timing of cell administration, and lack of controls for the presence of microvascular obstruction.

As reported in this issue of Circulation Research, Penn and coworkers now embark on fresh ground in 2 ways: First, by using an allogeneic bone marrow–derived stem cell product, and second, by using a catheter-based microneedle adventitial delivery system to eliminate some of the uncontrolled variables discussed above in patients 2 to 5 days after primary percutaneous coronary intervention for acute myocardial infarction. The strategy of injecting an allogeneic cell product should eliminate the heterogeneity inherent to all autologous...
cellular products by avoiding patient-specific, potentially confounding effects on cellular potency. The direct adventi-
tial delivery system bypasses the potential obstacles of cell
recruitment caused by impaired homing signals or micro-
vascular obstruction, which impedes cell entry into the
myocardium.

First, and most important in such phase I clinical trials,
both novel avenues for cell therapy in acute myocardial
infarction proved to be safe and feasible. The mesenchymal
cells, originally described by Verfaillie et al\textsuperscript{15} as bone
marrow–derived multipotent adult progenitor cells, were
experimentally shown to exert anti-inflammatory effects, to
protect cardiac myocytes from death, and to induce angio-
genesis,\textsuperscript{16} but they do not engraft long-term or transdifferen-
tiate into fully functional cardiac myocytes.\textsuperscript{17} As such, the
increase in cardiac function observed in the study by Penn
and colleagues\textsuperscript{14} further supports the paracrine hypothesis
also thought to be operative in the human heart after adven-
titial cell administration. More important, although the num-
ber of patients studied was small, no patient mounted a
humoral or cellular response characteristic of an immuno-
logic reaction, which suggests that the administration of this
allogeneic cellular product is feasible, without untoward
effects. However, caution should be exerted when these
patients are rechallenged with a repetitive allogeneic cellular
therapy or if they must undergo organ transplantation.

Like-
wise, injection of the cells through the coronary arterial wall
into the adventitia did not elicit demonstrable negative effects
on coronary blood flow, nor did it induce significant pericar-
dial effusions. However, patients were highly selected on the
basis of coronary anatomy suitable for positioning the mi-
croneedle catheter, and segments with severe and calcified
disease were avoided, thus limiting the generalization of the
conclusion that this method of cell delivery is indeed safe.

Overall, in the present study, the observed improvement in
ejection fraction was considerable and appeared to be rather
homogeneous, specifically in those patients with a baseline
ejection fraction <45\%. However, of note, only 1 of the 19
cell-treated patients received aldosterone antagonist treat-
ment, which is well established to modify remodeling pro-
cesses in patients with large myocardial infarctions. In
addition, the group of patients showing the most prominent
improvement in contractile function was also the group with
the longest time delay between symptom onset and acute
reperfusion therapy and thus might have derived more benefit
from additional cell administration. Therefore, larger patient
cohorts with accompanying state-of-the-art medical treatment
will be necessary to confirm the exciting data obtained in this
phase I trial. The finding of a significant contractile recovery
specifically in patients with depressed left ventricular func-
tion at baseline essentially confirms a number of previous
clinical studies that demonstrated an inverse relationship
between the absolute improvement in cardiac function after
BMC administration and baseline ejection fraction.\textsuperscript{18–20} If
one assumes that decreased baseline ejection fraction reflects
larger infarct sizes a few days after successful reperfusion
therapy, these intriguing findings might again be well ratio-
nalized by the 25-year-old observation that the compensatory
reserve capacity of the ventricular myocardium after infarc-
tion depends on infarct size and that inadequate adaptation of
the capillary vasculature is the major underlying mechanism.\textsuperscript{9}

Thus, if the vasculature is the major paracrine therapeutic
target of BMCs administered to the infarcted heart, one would
expect that BMC therapy would have the greatest impact in
patients with large infarcts by increasing capillary density and
myocardial perfusion in the infarct border zone. As such,
BMC therapy might be specifically tailored to patients at risk
for adverse left ventricular remodeling after acute myocardial
infarction. Reassuringly, this is also the patient cohort in need
of additional therapeutic interventions, given their still high
mortality even with acute reperfusion therapy and secondary
pharmacological preventive measures.

Interestingly, although the number of patients studied was
limited, patients receiving the highest number of cells did not
respond more favorably than patients receiving the half-
maximal dose. This observation is reminiscent of recent data
reported by Losordo et al,\textsuperscript{21} who showed that intramyocardial
injection of a lower number of CD34\textsuperscript{+} cells was superior to
injection of a higher number of cells in patients with
refractory angina. It is conceivable that the niche in the
human heart is limited in its capacity to retain cells injected
directly into the myocardium or into the adventitial space of
epicardial arteries. No such association has been observed
previously when cells were administered into the coronary
artery. However, the adventitial injection technique of a
homogeneous allogeneic cellular product now for the first
time allows for establishment of a potential dose-response
relationship in cell therapy in patients with acute myocardial
infarction. Moreover, by bypassing potential obstacles of cell
recruitment caused by microvascular obstruction, total distal
vessel occlusion, and lack of an intact homing signal–BMC
surface receptor interaction required for extravasation of
intra-arterially administered cells, the adventitial cell-delivery
technique may add a novel dimension to cell therapy of the
heart in both acute and chronic heart failure patients. Because
the technique is standard in interventional cardiology, and
handling and maneuvering the needle injection catheter is
similar to using balloon dilation catheters and does not
require additional imaging modalities, adventitial cell deliv-
ery might also be a rather cost-effective and straightforward
alternative to using catheter-based intramyocardial injections
via the left ventricular cavity. However, before its widespread
application, the safety of puncturing the coronary arterial wall
with a small needle for cell delivery into the adventitial space
must be established in larger patient cohorts.

In general, clinical phase I studies, besides showing feasi-
bility and safety, should also be viewed as hypothesis
generating. As such, the trial performed by Penn and col-
leagues\textsuperscript{14} may also open up other novel avenues for cell
therapy in cardiovascular disease. Patients with non–ST-
elevation myocardial infarction and preserved left ventricular
function are at considerable risk of experiencing subsequent
ischemic events. In fact, event rates at 1 year do not differ
from those of patients with ST-elevation myocardial infarc-
tion. Given that circumstantial evidence supports the notion
that the vasculature represents the major therapeutic target of
BMCs, whether autologous or allogeneic, the adventitial
delivery of the cell product may be well suited to improve
coronary vascular function in patients with acute coronary syndromes, in whom the limited myocardial ischemic damage may not be sufficient to attract intra-arterially administered cells into the perivascular compartment. Indeed, BMC administration was shown to profoundly improve coronary flow reserve in patients with acute myocardial infarction.22 If such an effect could also be achieved by adventitial cell delivery, one might selectively target cell administration along the culprit artery in patients with acute coronary syndromes regardless of ischemic injury to the heart to potentially limit the occurrence of subsequent ischemic events.

Disclosures

A.M.Z. is co-founder of t2cure.

References


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