Cell Therapy in STEMI: closing the clinical gap

Disclosure information: t2cure (co-founder, advisor)
SanofiAventis (SAB)
The Heart is a Regenerating Organ

Undisputable Evidence from DNA Integration of C-14 – generated during nuclear bomb testing during cold war -

Bergmann O et al., Science 2009; 324:98-102
Activation of endogenous regeneration by bone marrow-derived cells

A

MCM+/ZEG+ → OH-Tam x 14d → MCM+/ZEG+ → MI → 8wks

Bone-marrow Cell Harvest → Intramyocardial Cell Injection

βgal
GFP

B

Sham | MI | MI + c-kit

GFP+ = existing cardiomyocytes
LacZ+ = newly formed cardiomyocytes

Lofredo/Steinhauser et al, Cell Stem Cells 2011
Metaanalysis of randomized and cohort studies of progenitor cell therapy in ischemic heart disease

N = 976; overall treatment effect + 3.7 percentage points increase in LV-EF (p < 0.001)

Abdel-Latif, Arch Intern Med 2007; 167:989
Cell Therapy for STEMI

- The patient population at risk post-AMI
- Effects of cell therapy in patients at risk
- Derivation of the clinical benefit
LV contractile recovery within 1 week after successful reperfusion determines clinical outcome in STEMI

There is no linear correlation between mortality and ejection fraction after AMI!
VALIANT

Valsartan in Acute Myocardial Infarction Trial

- 14703 patients
- STEMI
- 0.5 - 10 days
- **EF < 40%**
- Killip I-III
- Diuretics 60%,
- Beta-Blocker 71%

Probability of cardiac death, re-MI rehospitalisation for heart failure

23% in 1 year
30% in 2 years

NEJM 2003, 349: 1893-1906
Cell Therapy for Ischemic Heart Failure

The patient population at risk post-AMI

Effects of cell therapy in patients at risk
Enhanced contractile recovery by BMC is confined to patients with failed initial recovery.

Baseline LVEF by QLVA

- EF below median (≤ 48.9 %)
  - Placebo: 2.5 ± 1.1
  - BMC: 7.5 ± 1.1
- EF above median (> 48.9 %)
  - Placebo: 3.7 ± 0.7
  - BMC: 4.0 ± 0.6

p for interaction = 0.020

Enhanced contractile recovery by BMC in patients with failed initial recovery – results of recent controlled trials

**REGENT trial**

**FINNCELL trial**

![Box plots comparing changes in EF (Ejection Fraction) for BMC and Placebo groups](image)

- **Controls (N=20)**: p=0.73
- **BMC (< median)**: p=0.007

**Change in EF (%)**

- **< median (BMC)**: p = 0.04

*Courtesy of M Tendera, European Heart Journal, 2009*

*Courtesy of H. Huikuri, European Heart Journal, 2008*
Adverse remodeling is confined to patients with failed initial recovery of EF and abrogated by BMC therapy.

Baseline EF: 39 ± 1.9 %  
Baseline EF: 56 ± 2.3 %

Change of endsystolic volumes over time (MRI)

**EF < median**  
**EF > median**

Dill et al., AHJ 2009
Intracoronary BMC Administration Profoundly Modifies LV Remodeling

Interaction between LV ejection fraction and endsystolic volume

\[ \text{EF} \leq 48.9\% \]
\[ p = 0.007 \]

BMC
Reperfusion
Placebo
pharmac. Rx
no therapy

EJHF 2009
Do beneficial effects of BMC therapy on adverse remodeling translate into clinical benefit?

- Therapies preventing adverse remodelling...
  - ACEI, ARB, β-Blocker, Aldosteron-Ant.

- Cardiovascular Events
  - Mortality ↑
  - Ischemic events ↑
  - Rehospitalization for heart failure ↑

- Acute myocardial infarction

- Left Ventricular Remodeling
  - Ejection fraction ↓
  - End-systolic volume ↑
Adult Bone Marrow Cell Therapy Improves Survival and Induces Long-Term Improvement in Cardiac Parameters: A Systematic Review and Meta-Analysis
Vinodh Jeevanantham, Matthew Butler, Andre Saad, Ahmed Abdel-Latif, Ewa K. Zuba-Surma and Buddhadeb Dawn

**Background** - Despite rapid clinical translation and widespread enthusiasm, the therapeutic benefits of adult bone marrow cell (BMC) transplantation in patients with ischemic heart disease (IHD) continue to remain controversial. A synthesis of the available data is critical to appreciate and underscore the true impact of this promising approach.

**Methods and Results** - A total of 50 studies (enrolling 2,625 patients) identified by database searches through January 2012 were included. Weighted Mean Differences for changes in left ventricular (LV) ejection fraction (LVEF), infarct size, LV end-systolic volume (LVESV), and LV end-diastolic volume (LVEDV) were estimated using random effects meta-analysis.
**BMC therapy post-AMI**  
**Improved clinical outcome in meta-analysis**

Table 6. Clinical outcomes in BMC-treated patients compared with patients receiving standard therapy

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Peto OR</th>
<th>95% Confidence Interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>0.39</td>
<td>0.27 to 0.55</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Cardiac deaths</td>
<td>0.41</td>
<td>0.22 to 0.79</td>
<td>0.005</td>
</tr>
<tr>
<td>Recurrent MI</td>
<td>0.25</td>
<td>0.11 to 0.57</td>
<td>0.001</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0.52</td>
<td>0.27 to 1.00</td>
<td>0.05</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>0.34</td>
<td>0.12 to 0.94</td>
<td>0.04</td>
</tr>
<tr>
<td>In-stent restenosis</td>
<td>0.87</td>
<td>0.47 to 1.62</td>
<td>0.66</td>
</tr>
<tr>
<td>TVR</td>
<td>0.83</td>
<td>0.55 to 1.23</td>
<td>0.35</td>
</tr>
<tr>
<td>CVA</td>
<td>0.28</td>
<td>0.08 to 1.07</td>
<td>0.06</td>
</tr>
<tr>
<td>VT / VF</td>
<td>1.14</td>
<td>0.52 to 2.53</td>
<td>0.74</td>
</tr>
</tbody>
</table>

N = 2625

Abbreviations: BMC, bone marrow cell; CVA, cerebrovascular accident; MI, myocardial infarction; OR, odds ratio; TVR, target vessel revascularization; VF, ventricular fibrillation; VT, ventricular tachycardia.
5 years clinical follow up
- Kaplan Meier Analysis -

Death & rehospitalization for heart failure

Event-free survival (%)
(death, rehospitalization f. heart failure)

Days follow-up

BMC
Placebo

p = 0.082
(log rank)
5 years clinical follow up
- Kaplan Meier Analysis -

Death

Event-free survival (%)
(death)

Days follow-up

Placebo

BMC

p = 0.081
(log rank)
Baseline LVEF determines long-term effects of BMC therapy in STEMI

**Baseline LVEF**

- **LVEF ≤ 45%**
  - BMC
  - Placebo
  - *p* = 0.026

- **LVEF > 45%**
  - BMC
  - Placebo
  - n.s.
Closing the gap in cell therapy of STEMI

In patients with acute post-infarction heart failure despite successful reperfusion therapy

a large-scale clinical endpoint trial is warranted to document the effects on mortality and morbidity
BAMI Clinical Trial Design
(ESC Cell Therapy Trial Consortium)

The effect of intracoronary reinfusion of bone marrow-derived mononuclear cells on all-cause mortality in STEMI

- 1:1 randomized, controlled, no placebo group
- intracoronary BMC administration vs. standard care
- approx. 3000 patients, event-driven trial design
- primary endpoint: all-cause mortality
- Inclusion criterion: LVEF < 45% 3-6 days after successful reperfusion by quantitative echo core lab analysis
- Aim: to reduce 2-year mortality by 25%
- anticipated mortality in control group: 11.5% at 2 years
- 11 participating European countries
- 6 core cell processing facilities across Europe
- first patient in: Q4 / 2012
Clinical Trial Design

Patients with acute myocardial infarction post primary PCI

Screening phase

N = 3000 eligible AMI patients
3-6 days post primary PCI
Central reading of echocardiography (EF ≤45%)
-> randomisation 1:1 = day 0

Group 1: Control n= 1500
No intervention = day 1

Group 2: BM-MNC, n= 1500
Bone marrow aspiration = day 1

Intracoronary infusion of BM-MNCs = day 1, day 2 or day 3 (depending on transportation and cell processing schedule) 4-8 days post PCI

Day 30 ± 3 days: Telephone follow-up
Month 3: Telephone follow-up
Month 6: Site visit follow-up
Every 3 months: Telephone follow-up
End of study visit

Day 30 ± 3 days: Telephone follow-up
Month 3: Telephone follow-up
Month 6: Site visit follow-up
Every 3 months: Telephone follow-up
End of study visit
Cell processing centers and patient distribution

Cell Processing Centers

- The Royal London Hospital, London, UK
- Hopitaux de Paris, Hopital Saint Louis, Paris, France
- Hospital Gregorio Maranon, Madrid, Spain
- Rigshospitalet University Hospital, Copenhagen, Denmark
- Universitaire Ziekenhuizen, Leuven, Belgium
- BSD, Institute for Transfusion Medicine Frankfurt, Germany
Factors influencing function of autologous BMC

Cell intrinsic factors
- Patient characteristics
  - Age
  - Diabetes
  - Heart failure
  - Acute MI

Extrinsic factors
- Cell preparation:
  - Purity
  - Contaminations (e.g. Red blood cells, granulocytes?)
- Cell storage:
  - pH (NaCl)
  - Temperature
  - Serum vs Plasma
  - Heparin
  - Nutrients/Metabolism

Cell functionality
- Survival
- Migration/Homing
- Paracrine activity
- Differentiation capacity
- Colony formation
Migratory / Invasion Capacity of BMC: Effects of Heparin

In-vitro migration assay

Ischemia

Cytokines, e.g. VEGF, SDF-1

Control

Heparin

Bivalirudin

![Graph showing invaded cells (10^3/10^6) for control, heparin, and bivalirudin at different concentrations: 0.05 U/ml, 0.1 U/ml, 0.5 U/ml, 1 U/ml, 2 U/ml, 20 U/ml, 7.5 µg/ml, 15 µg/ml, 30 µg/ml.](image)

*p<0.05 vs Control; n≥3

Circ Res 2012
## Heparin Use in Clinical BMC Trials in AMI

### Ficoll isolated BMC trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of pts.</th>
<th>Cells</th>
<th>Heparin in Final Cell Product</th>
<th>Primary Endpoint</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASTAMI</td>
<td>100</td>
<td>i.c.; BM-MNC vs. standard therapy</td>
<td>5 U/ml</td>
<td>LVEF (SPECT)</td>
<td>(-) after 6 / 12 months</td>
</tr>
<tr>
<td>BONAMI</td>
<td>101</td>
<td>i.c.; BM-MNC vs. standard therapy</td>
<td>No heparin</td>
<td>Vitality (SPECT)</td>
<td>(+) vitality after 3 months; (-) LVEF</td>
</tr>
<tr>
<td>FINCELL</td>
<td>80</td>
<td>i.c.; BM-MNC vs. medium</td>
<td>heparinized serum</td>
<td>LVEF (QLVA, echo)</td>
<td>(+) LVEF after months</td>
</tr>
<tr>
<td>HEBE</td>
<td>200</td>
<td>i.c.; BM-MNC vs. peripheral MNC vs. standard therapy</td>
<td>20 U/ml</td>
<td>reg. LV-function (MRI)</td>
<td>(-) after 4 months</td>
</tr>
<tr>
<td>Janssens-Trial</td>
<td>67</td>
<td>i.c.; BM-MNC vs. NaCl + serum</td>
<td>No heparin</td>
<td>LVEF (MRI)</td>
<td>(+) reduction infarct size; (+) regional LV function</td>
</tr>
<tr>
<td>Plewka et al</td>
<td>60</td>
<td>i.c.; BM-MNC vs. standard therapy</td>
<td>?</td>
<td>LVEF (echo)</td>
<td>(+) LVEF after 6 months</td>
</tr>
<tr>
<td>REGENER</td>
<td>200</td>
<td>i.c.; BM-MNC vs. CXCR4+ BM-MNC vs. standard therapy</td>
<td>No heparin</td>
<td>LVEF (MRI)</td>
<td>(++) LVEF after 6 months in cell treated groups</td>
</tr>
<tr>
<td>REPAIR-AMI</td>
<td>204</td>
<td>i.c.; BM-MNC vs. medium</td>
<td>No heparin</td>
<td>LVEF (QLVA)</td>
<td>(+) LVEF after 4 months; (+) after 12 &amp; 24 months</td>
</tr>
</tbody>
</table>
Functional capacity of the applied BMC predicts clinical outcome at 5 years

Assmus et al., AHA 2012

Event-free survival [%] (cardiac, cardiovascular and unknown death, rehospitalization for heart failure)

SDF-1-ind. migration > mean

SDF-1-ind. migration ≤ mean

$\text{Years follow-up}$

$\text{Numbers at risk}$

$\text{Migration} \leq 170$

53 51 49 48 45 44

$\text{Migration} > 170$

48 48 48 46 45 42

$p = 0.01$ (log rank)
Premedication prior to BM-MNC application

• ASS and Clopidogrel / Prasugrel / Ticagrelor should be loaded prior to coronary angiography according to standard guidelines.

• Bivalirudin should be given prior to the cell administration procedure. Heparin including low molecular weight heparin is not allowed during cell administration. Syringes and catheters may not be flushed with heparin containing solutions.
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