EuroIntervention

Cardiovascular repair and regeneration 2008: the Fourth International Conference on Cell Therapy for Cardiovascular Disease (IC3D)

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On January 16-18, 2008, The International Conference on Cell Therapy for Cardiovascular Disease (IC3D) held its fourth annual meeting in New York City at the campus of Columbia University. This meeting has set its sights on cellular and molecular approaches to cardiovascular repair and regeneration, choosing to be a comprehensive "stand-alone" forum for investigators, clinicians and the many others who are engaged, or seeking to be engaged in the field. Advances on multiple scientific fronts have brought insights into mechanisms of tissue healing and uncovered new potential for cellular recovery and replacement. With the unabated rise in the prevalence of cardiovascular disease, the interventional community is increasingly faced with caring for patients with chronic coronary, myocardial and conduction system diseases. It therefore is incumbent upon us to remain current with developments in regenerative cardiology, which, in fact, are many. In recent years IC3D has integrated basic, translational and human studies into a clinical disease orientation. The program (www.crf.org) and numerous presentations (www.tctmd.com) for IC3D 2008 are accessible online; highlights are excerpted in this article. Due to limited space, and in an attempt to submit material of clinical relevance, the significant and exciting data presented by scientists from the cell biology and tissue engineering communities have been omitted from this discussion.

ST-elevation myocardial infarction

The opening session addressed the maladaptive mechanisms of recovery from post-ischaemic injury in humans, and their potential as targets for repair strategies. Developmentally, cardiac growth parallels angiogenesis, and paracrine mechanisms coordinate this relationship. Myocardial recovery from acute injury (as well as progression from chronic hypertrophy to heart failure) depend on paracrine signalling.

Since the improvement in LV function cannot be attributed to the incorporation of progenitor cells into tissue, growth factors are thought to stimulate repair. Adding to the common families of VEGF and FGF, other potent growth factors and cytokines have been identified (Akt, NK102, Fstl1, GDF15, myostatin, BMP2, Cyclin A2, HASF, Dkk-1, to name a few) and show promising effects on reducing infarct size and augmenting LV function in pre-clinical studies. Moreover, mechanisms of action have been further elucidated, in particular for SDF-1 and HGF, which, in addition to increasing vascular density, are now known to decrease infarct size through preservation of cardiac myocytes and recruitment of cardiac like stem cells into the infarct zone. Despite the largely negative clinical findings observed with G-CSF (perhaps owing to its pro-inflammatory features and cleavage of CXCR4), the application of novel mobilising agents or other cytokines is expected to increase in future clinical studies.

Adult stem cell studies were highlighted by updates of larger data-sets (bone marrow-derived mononuclear cells) and by important observations from early phase trials (bone marrow-derived autologous and allogeneic cells, as well as adipose-derived progenitors). While differences remain among the studies, such as in patient population, cell product and route of administration (intravenous administration of allogeneic bone marrow-derived mesenchymal cells vs the "stop flow" technique of intracoronary infusion through an OTW balloon)

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consistent trends in outcomes are apparent. Improvement in LV function, with some variability, continues to be seen in both regional and global assessments. Measured differences in LV function between clinical trial may be explained by disparities in: 1) cell preparation, 2) LV assessment methods (radiographic, echocardiographic, radionuclide or magnetic resonance imaging) and 3) timing of assessment (with respect to STEMI onset and study intervention). As in past meetings, concerns were raised as to the significance of changes seen in LVEF (absolute increases of 3-5% above baseline levels of 45-50%) and their impact on clinical endpoints. Discussions were also focused on what are the appropriate end-points of AMI cell therapy trials. The linear relationship between post-STEMI EF and mortality has been challenged, especially in EF's <50% within one week of the index event. Moreover, progenitor cell administration is associated with enhanced LV contractile recovery and improved coronary flow reserve, and it appears to mollify adverse left ventricular remodelling in patients at risk.

These findings, added to encouraging observations from the largest randomised clinical study, fully justify the conduct of a large (800-1000 patient) Phase 3, multicentre, randomised, placebo-controlled trial to primarily assess clinical efficacy, and is soon to begin in Europe.

Angiogenesis and tissue ischaemia

A common thread which connects many pathogenic mechanisms is cellular ischaemia, and special emphasis was given to microvasculature as the principal target in repairing ischaemic tissue. In this regard, human endothelial progenitor cells (EPCs) and their potential therapeutic utility in healing from tissue injury and wounds have come to the forefront, and the breadth of discovery arising from studies of EPCs (or related progenitors such as, CD34+ bone marrow-derived cells) has been extensive. Several speakers elucidated known, and proposed, mechanisms of functional effects of EPCs, among them paracrine activity (via pro-angiogenic and anti-apoptotic factors VEGF, IGF-1, HGF), enhancement of endogenous repair through the actions of thymosinß4 and HGF), positive tissue remodeling (reduction in fibrosis and scar formation) and modulation of inflammation. Novel methods were put forward for enhancing functional effects of EPCs, including topical gene-therapy (to mimic signalling pathways in the embryo) and "priming" with agents such as Angiopoietin-1. An exciting observation of synergism between EPCs and adipose-derived cells was reported, supporting the enhanced capacity to assemble stable vessels by the combination of cell lines.

In light of compelling associations between circulating EPC levels and both endothelial function and atherosclerosis risk score, assessing EPCs in patients may be of great importance. As several speakers pointed out, this may be especially so if we are to understand, and predict, the responses of patients to therapies which incorporate EPC-based technology, as with "EPC-capture" designed coronary stents.

Clinical ischaemic diseases

Results from clinical studies with various adult angiogenic progenitors (autologous BMD mononuclear, CD133+, mobilised CD34+ and immunoselected BMD mesenchymal precursor and adipose-derived stem cells) in patients with critical limb (CLI) and chronic myocardial ischaemia (CMI) were reported. These trials are at an earlier recruitment stage than those in STEMI patients, and positive clinical observations are therefore still preliminary. In patients with CMI, one randomised placebo-controlled trial (ACT34-CMI, >150 subjects) is of particular importance. As of this writing, enrolment has been completed and primary efficacy data are expected by late 2008. Also reported were results from a Phase-II prospective, randomised, controlled trial in 40 patients, in which CABG & intramyocardial injection of CD133+ BMD cells resulted in better LV ejection fraction and perfusion than CABG alone. For patients with CLI, several randomised studies (up to 90 patients) using autologous BMD cells were described. Preliminary, and preceding, data are very encouraging for limb salvage and avoidance of major amputation in patients ineligible for revascularisation.

Novel strategies for treating chronic (and acute ischaemia) are emerging. A new cell product has drawn considerable attention: adipose-derived stem cells (ADSC) and methods for their rapid procurement (using minimally invasive procedures) and high cell yield were described. Such cells appear very suitable for clinical study; two ongoing trials were reported in preliminary form for CMI (PRECISE) and STEMI (APOLLO). Additionally, options for catheter-based delivery methods have expanded for the CMI patient. Added to guided endoventricular techniques (i.e., NOGA, the "standard-bearer"), we can now consider both selective anterograde (SEACOAST) and retrograde (TELECORI RA) coronary infusion. Presentations from both of these studies describe important gains in symptoms and objective measures of ischaemia in patients with refractory angina.

Left ventricular dysfunction and congestive heart failure

The themes for the closing day of IC3D moved to "Restoration of myocardial function: current clinical observations" and "The future of cardiovascular repair and regeneration: integration and collaboration". Status updates of completed clinical trials such as FOCUS-HF (BMD mononuclear cells), CAuSMIC (autologous skeletal myoblasts), MYOHEART (autologous skeletal myoblasts) and CD133+ cells as adjunct therapy to CABG all conveyed promising clinical trends for patients with moderate-to-severe LV dysfunction and CHF. Positive changes in such parameters as quality of life assessed by NYHA Classification and Minnesota Living with Heart Failure Questionnaire (FOCUS-HF, CAuSMIC, MYOHEART), six minute walk test (MYOHEART), MVO2 (FOCUS-HF) were noted. Improvements in other parameters were reported, such as in viability (unipolar voltage) by NOGA® mapping and in LV remodelling (echocardiography) and perhaps most importantly, safety and feasibility no longer appear to be issues of question with these techniques, in this patient population. To further define the significance of these findings, Phase 2-3 randomised, controlled trials have been initiated, with enrolment of 150-350 subjects in each study.

Several caveats are relevant for these studies, and are in keeping with data presented for STEMI and chronic ischaemia. First, BMD

cell function was observed to be severely impaired in the CHF population and appear to be correlated with age. Second, data suggest a relationship between the function of certain cell types and clinical outcomes. Third, across the board, the risk for severe ventricular arrhythmias is low, including in the myoblast population, especially when corrected for baseline arrhythmic status.

In looking at early phase studies for ischaemic cardiomyopathy and CHF, BMD mesenchymal cells are a highly promising cell source for cardiac therapy and will be the study agent of a multicentre surgical based trial. And, as an alternative to *in vitro* enhancement of the cell function, pretreatment of target tissue using protein, gene or cell based gene therapy may improve stem cell homing and efficacy. Furthermore a novel stategy for tissue preparation. The application of low energy shock wave to the LV is one such strategy, and has been incorporated into the "Cell Wave Trial".

The final highlight of IC3D emphasised the critical importance of functional collaborations. These have taken on the form of governmental initiatives (NIH SCCT and CCTRN; Brazilian Ministry of Health), multisourced initiatives (REPAIR-AMI-2) and industry sponsored initiatives (MAGIC, SELECT-AMI, MARVEL). The value of such efforts cannot be overstated, especially in a field that has not yet reached commercialisation.

Summary

The principal lessons and take-home points from IC3D are: 1) clinical trials are in an expansion stage, being constructed upon the substantial foundation of the international experience of the last 6-7 years, and now looking at hard clinical endpoints, 2) catheter-based cell-delivery is likely to be the mainstay of clinical trials and, in time, clinical practice, 3) the coming year will bring light to techniques for enhancing cell function (autologous or allogeneic), improving tissue receptivity to cell delivery and facilitating the performance catheter-based procedures.

While the role of cell-therapy in clinical practice is yet to be established, signals from existing data indicate that engagement of the interventional cardiology community in this field should be expanded.