Stem Cell Therapies for CLI
Promising Alternative or Excessive Hype?

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Therapeutic Angiogenesis

- Gene Therapy:
- Cell Based Therapy:

Therapeutic Angiogenesis

- Gene Therapy: the use of genetic material (usually DNA) to manipulate a patient’s cells for the treatment of disease.
  - hypoxia-inducible factor-1 (HIF-1α)
- Cell Based Therapy:
Therapeutic Angiogenesis

- **Gene Therapy:** the use of genetic material (usually DNA) to manipulate a patient’s cells for the treatment of disease.
  - hypoxia-inducible factor-1 (HIF-1α)

- **Cell Based Therapy:** the infusion or transplantation of whole cells that have the capability to differentiate into a number of different cells.
  - Allogeneic: from external source such as placenta, umbilical cord
  - Advantage: can be engineered and stored so that it can be used when needed
  - Disadvantage: potential for immunogenicity
  - Autologous: Bone Marrow
  - Advantage: No issues with immunogenicity
  - Disadvantage: must be prepared either on site, or more commonly sent out and returned in 3-12 days

The WALK Trial

- Hypoxia-inducible factor 1 (HIF-1) is an inducible transcriptional regulatory factor that plays a principal role in the cellular response to changes in oxygen tension and regulates genes involved in angiogenesis.

- This study tested the efficacy of intramuscular administration of Ad2/HIF-1α/VP16, an engineered recombinant type 2 adenovirus vector encoding constitutively active HIF-1α, in improving walking time in patients with intermittent claudication.

  - Compared with placebo, Ad2/HIF-1α/VP16 treatment did not improve peak walking time, claudication onset time, or ability to walk.

  - There was no change in the ankle-brachial index, or walking ability assessed by questionnaire.


Results of Gene Trials

- To date, placebo-controlled clinical trials of angiogenic gene therapy have failed to demonstrate efficacy in patients with peripheral artery disease despite encouraging signals in preclinical models and preliminary human studies.

  - Phase II trials promising, Phase III trials negative
Angiographic Demonstration of Neoangiogenesis After Intra-arterial Infusion of Autologous Bone Marrow Mononuclear Cells in Diabetic Patients With Critical Limb Ischemia

• Autologous bone marrow mononuclear cells (BMMNC) infused in 20 patients with diabetes and CLI
• After 12 months, all patients improved in the Rutherford classification, UT diabetic wound scale and ABI of target limb.


Autologous Transplantation of Bone Marrow Cells

Autologous Transplantation of Bone Marrow Cells

Therapeutic Angiogenesis

Long-Term Follow-Up in TACT

- Median follow-up for surviving patients was 25 months
- 3 year overall survival:
  - For patients with atherosclerotic PAD was 80% (11 of 74)
  - For patients with TAO (Buerger’s disease) was 100% (41)
- 3 year amputation free rate was:
  - 60% in patients with PAD
  - 91% in patients with TAO
- There was no unwanted neovascularization


Therapeutic Angiogenesis by Cell Transplantation [TACT] trial

B Amputation-free survival

Ixmyelocel-T is a autologous, patient-specific, expanded, multi cellular therapy. In preclinical studies, it has been shown to have multifunctional properties including: tissue remodeling, immune modulation, and the promotion of angiogenesis.
Cellular Therapy With Ixmyelocel-T to Treat Critical Limb Ischemia: The Randomized, Double-blind, Placebo-controlled RESTORE-CLI Trial

- In conclusion
  - there were no major safety issues related to ixmyelocel-T treatment in patients with no-option CLI.
  - Treatment with ixmyelocel-T improved Time To Treatment Failure (TTF) in treated patients as compared with controls.
  - These results suggest that treatment with ixmyelocel-T has the potential to be a promising treatment option in patients with CLI who are unable to undergo revascularization.
  - Based on these data, a larger phase 3 pivotal trial is warranted.

**Aastrom BioSciences ends drug trial, to cut half its workforce**

Aastrom BioSciences Inc. said it would end a long-running drug trial and cut half its workforce, the latest sign of trouble for the company that has struggled to develop therapies despite a $200 million investment from Microsoft Corp.

May 27, 2013

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**Placental-Derived Adherent Cells for the Treatment of Peripheral Vascular Disease: FDA/PEI-Approved Phase I Clinical Trials**

Pluristem Therapeutics

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**Patient Summary**

- 27 CLI patients
  - 3-low dose (~200x10^6)
  - 13-intermediate dose (~300x10^6)
  - 11-high dose (~600x10^6)
- 5 patients received the high dose in two courses of the intermediate dose two weeks apart
- Rutherford Category 5 - 10 patients
- Rutherford Category 4 - 17 patients

**Germany**

- 15 subjects - 10 males and 5 females, aged 40-80 years.

**USA**

- 12 subjects - 11 males and 1 female, aged 51-79 years.

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**Administration of PLX-PAD Cell**

- 30 or 50 IM injections
- above/below the knee of the afflicted limb
- Treatment takes ~20 min to complete
Safety—12 Months Follow-Up

No significant safety issues
PLX-PAD cells can be given IM safely
No evidence of malignant transformation

**Methodology** | **Results**
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Ultrasound of Abdominal and of both legs at 6 months, 12 months and 24 months | No malignancies reported
Serum sample levels of tumor markers (PSA, CEA, CA125, AFF and NSE) at 6 months, 12 months and 24 months | Serum levels were found to be within normal range

PLX-PAD – 12 month AFS

85% Amputation-Free Survival (AFS)
(4 amputations/deaths out of 27 Patients)

In comparison to published data
68% (TAMARIS Phase III)
58% (Historical data)

Current Stem Cell Trials for CLI

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4 other small trials, mostly international. Some using adipose tissue.

Conclusions

• Cell based therapy has promise in the treatment of patients with peripheral arterial disease (claudication and CLI)
• To date, most studies have used autologous Bone Marrow Mononuclear Cells
• Several studies are ongoing/recruiting.
• One study has used placental stem cells and larger studies are planned for claudication, CLI and Buerger’s disease

Thanks

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