Newest Stem Cell Therapies are Effective in Treating Lower Extremity Ischemia

Marianne Brodmann, MD
Division of Angiology, Medical University Graz, Austria

Disclosure Statement of Financial Interest

I, (insert name) DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

CLI

- Ischemic rest pain
- Ulcers
- Gangrene

CLI_Therapeutic options

- Revascularization _ Endovascular/Surgery
  - Retrograde approach/Foot arteries/Pedal puncture
  - New endovascular techniques_Deep venous arterialization
- Within 1 yr of presentation
  - 30% major amputation
  - 20% unresolved pain, tissue loss
  - 25% will die

CLI unsuitable for revascularization... 50% major amputation at 1 yr

Stem cell for No option CLI

- Cell therapy is proposed endovascular or surgic;
- The therapy with stem compared with protein properties, but also the substances.

Stem cell for No option CLI

The primary benefit of SCT is

- to induce therapeutic neovascularization
- promote collateral vessel formation to increase blood flow in the ischemic limb and soft tissue

Existing evidence provides a solid rationale for ongoing in-depth studies aimed at advancing current SCT that may change the way PAD/CLI patients are treated.


Stem cell for No option CLI

The sources and types of stem cells/progenitor cells for therapeutic angiogenesis

- ADSC: adipose-derived stem cell
- ALDHbr: aldehyde dehydrogenase bright
- BM: bone marrow
- EPCs: endothelial progenitor cells
- MNC: mononuclear cell
- MSC: mesenchymal stem cell
- PB: peripheral blood
- UCB: umbilical cord blood

1. Intramuscular ↑↑↑
2. Intraarterial      ↑↑
3. Subcutaneous ↑

Stem cell for No option CLI.Results

Bone marrow mononuclear cells

- FIH (small sample size) showed a positive effect on the time to amputation, amputation-free survival, wound healing, ABI, TcPO2, distance of painless walk, pain at rest, and severity of limb ischemia (Rutherford category or Fountain stage)
- The multicenter placebo-controlled RCTs with intraarterial injection of BM-MNCs have shown no significant differences in the rate of major amputations in the JUVENTAS study [2] and amputation-free survival in the PROVASA study [3]
- explainable by that the cells would hardly reach the target tissue in the case of intraarterial infusion into considerably compromised arteries
- large share of the cells infused intraarterially is retained in the precapillary vasculature, thereby potentially interfering with the blood circulation

Bone marrow derived cells

- multipotent cells of the stroma of different tissues
- possible to use the allogeneic NSCs of healthy donors, which retained the ability to neovascularize
- Currently, the Clinical and Histologic Analysis of Mesenchymal Stromal Cells in AmPutations (CHAMP) trial is in progress
- Comparison of the therapeutic effects of intramuscular allogeneic MSCs and autologous BM aspirate injections
  - BM-MSCs and BM-MNCs was tested in 26 CLI subjects versus placebo.
  - ABI considerably increased 4 months after injection.
  - Technetium (99mTc) tetrofosmin scintigraphy: increased perfusion of the treated limbs
Cells from the peripheral blood and other alternative sources

- Stem cell mononuclear cells
  - Small RCTs demonstrated an increase in ABI and TcPO2 and better ulcer healing in the CLI and diabetes subjects after intramuscular injections of PB-MNCs.
  - Phase 3 of a pilot clinical trial using mobilized PB-MNCs (ClinicalTrials.gov NCT01833585) is completed.
  - Direct comparison of the BM-MNC and PB-MNC efficiencies gave rather contradictory data.
    - Intramuscular injection of BM-MNCs or PB-MNCs to 180 CLI subjects demonstrated a statistically significant increase in ABI in 106 and a decrease in ulcer size in 82. The PB-MNC dose, although the same, significantly increased the number of cell passages. Among the studies, good results were obtained for the PB-MNC dose, even when the dose was the same. Further studies are required to demonstrate the need for PB-MNC doses.

Cells from the peripheral blood and other alternative sources

- The mesenchymal stromal cells derived from alternative sources
  - PB-MNC cells
  - Preclinical studies: cells have shown proangiogenic, anti-inflammatory, and regenerative properties
  - PACE study: a phase 3 randomized double-blind multicenter multinational placebo-controlled parallel group study to evaluate the efficacy, tolerability, and safety of intramuscular injections of PLX-PRD cells for treating inflammatory CLI subjects with minor tissue loss (Rutherford category 2) up to the ankle level.

Stem cell for No option CLI_Results

- Endothelial progenitor cells (EPCs)
  - First time identified in the adult human peripheral blood as CD34-positive (CD34+) MNCs in 1997.
  - EPCs are isolated from PB-MNC cultures grown in a specialized VEGF-containing media.
  - Assessed in phases 1 and 2 as a multicenter clinical trial involving 17 CLI subjects.
  - Consistently, CLI severity according to Rutherford as well as the pain and size of skin ulcers 12 weeks after the treatment although a statistically significant data response was not obtained.
  - The safety and efficacy of CD34+ cell therapy is the same for 4 years after the treatment.
  - A phase 2 clinical trial confirms the safety, feasibility, and potential efficiency of the CD34+ cell grafting to CLI patients.

Stem cell for No option CLI_Results

- Adipose-derived stem cells (ADSCs) or adipose derived regenerative cells (ADRCs)
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  - Advantage: can be isolated from a small specimen of the human subcutaneous adipose tissue via minimally invasive procedures, including liposuction, and propagated ex vivo.
  - A clinical trial, ACellDREAM, involving seven CLI subjects has demonstrated that intramuscular injection of autologous ADSCs cause an increase in TcPO2 and wound healing rate.

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Stem cell for No option CLI_Results

Conclusion

- Although the cumulative data on the cell therapy of critical limb ischemia are most promising, more studies with larger cohorts are necessary to provide stronger safety and efficacy data on cell therapy.
- Assessment of the angiogenic potential of multipotent cells plays the key role in estimation of the purposefulness of cell therapy when treating ischemic diseases, since the angiogenic potential of the multipotent cells derived from healthy subjects differs from that of the patients suffering from atherosclerosis, chronic kidney disease, diabetes, and so on.
- An increased interest to the modification of angiogenic potential once again demonstrates that the assessment of cell activity, which is the background for standardization of a cell product, will be the decisive factor in demonstrating the efficacy and providing the reliable comparison with the other approaches to the treatment of CLI.
Thank you for your attention