Cellular Therapy vs Hematopoietic Cell Transplantation: Development of the Cellular Therapy Registry

Marcelo C. Pasquini, MD, MS
Outline

- What is cellular therapy?
- Cellular therapy related HCT
  - Donor cellular infusions
  - Mesenchymal stromal/stem cells
- Cellular therapy for *regenerative medicine*.
- Development of the Cellular Therapy Registry
  - Initial concept and implementation
- Data collection
  - Challenges and strategies.
- Q&A
THE TRUTH ABOUT STEM CELLS
THE HOPE, THE HYPE AND WHAT IT MEANS FOR YOU
Cellular Therapy
What is Cellular Therapy?

- Utilization of cells for treatment of human diseases.
- Transfusion and Hematopoietic cell transplantation (HCT) are cellular therapies.
- What are the differences?
  - Transfusion $\rightarrow$ **terminally differentiated** cells that survive in the recipient for a short period of time.
  - HCT $\rightarrow$ stem and progenitor cells **engraft** and **replace** the recipient’s bone marrow.
Terms and Definitions: Potency

- **Totipotency**: "total potential". Cells able to differentiate all cells in an organism including extraembryonary tissue. Ex: embryonic stem cells.

- **Pluripotency**: "potential for multiple outcomes". Cells able to originate cells of different lineages. Ex: mesoderm cells.

- **Multipotency**: cells able to originate several lineages. Ex: hematopoietic stem cells.
Stem Cells Potency

Examples:
- Circulatory System
- Nervous System
- Immune System

Oocyte → Totipotent → Blastocyst → Human Fetus

Pluripotent Inner Mass Cells
Embryonic Stem Cells (ES) Potency
Terms and Definitions

- **Stem cells**: cells able to self renew and differentiate into mature cells (potency).
- **Progenitor cells**: similar to stem cells but more limited.

<table>
<thead>
<tr>
<th></th>
<th>Stem Cell</th>
<th>Progenitor Cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self renewal</td>
<td>Unlimited</td>
<td>Limited</td>
</tr>
<tr>
<td>Potentiaility</td>
<td>Multipotent</td>
<td>Unipotent, sometimes multipotent</td>
</tr>
<tr>
<td>Maintenance of Self Renewal</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
Hematopoiesis Scheme

Stem Cells

Progenitor Cells

- T-lymphocyte
- B-lymphocyte
- NK cells
- Megakaryocyte
- Erythrocyte
- Granulocyte
- Monocyte
Terms and Definitions

- **Terminal differentiation**: cells that achieve maximum differential/maturation.

- **Committed cell**: maturing cells on a specific lineage path.

- **Transdifferentiation**: cells committed to one lineage differentiating into different lineages. Ex: blood cells → neurons (???).

- **Induced Pluripotent Cells (iPS)**: terminally differentiated cells induced to become pluripotent with in vitro manipulation.
Lineages derived from Human iPS cells

Takahashi K et al. Cell 2007, 131: 861-872
Hematopoietic Stem Cell Transplantation - Classification -

- **Donor**
  - Allogeneic
    - HLA-identical sibling
    - Other relative
    - Unrelated
  - Syngeneic
  - Autologous

- **Conditioning Regimen Intensity**
  - Myeloablative
  - Reduced Intensity
  - Non-myeloablative

- **Graft Source**
  - Bone marrow
  - Peripheral Blood
  - Umbilical cord blood

- **Graft manipulation**
  - Negative or positive selection
  - Ex vivo expansion
  - In vivo selection
Cellular Therapies
- Classification -

- **Autologous**, **Allogeneic**, **Syngeneic**
- **Single vs. Donor Pool**
- **Live or cadaveric**
- **Donor**
- **Tissue Specific**
- **Differentiated Stem cells**, **Progenitor cells**
- **Manipulated cells (iPS)**
- **Cell Type**
- **Bone marrow**, **Peripheral blood**, **Umbilical cord blood**
- **Placenta**, **Umbilical cord**, **Amniotic Fluid**
- **Cardiac, Skin, Liver...**
- **Graft Source**
- **Unmanipulated vs. Cell separation**
- **Cells in solution**
- **tissue engineering**
- **Graft manipulation**
- **Infusion type**
- **HLA matching**
- **Recipient preparation**
- **Other Classifications**

CIBMTR®
Hematopoietic Cell Transplantation Course

Complications:
- Acute and/or chronic GvHD
- Viral infections
  - CMV, VZV, PCP, IP
- Bacterial infections
  - HSV, mucositis
- Secondary tumors, cataracts, endocrine changes, QoL

Blood & Marrow Changes:
- PBSC/BM harvests in ABMT

BMT Process:
- Donor search or obtain autologous stem cells

Supportive Therapy:
- Red cell transfusions
- Platelet transfusions
- Donor search or obtain autologous stem cells
- Chemo stem cells
- Immunotherapy
- DHAP and GF and PBSC

Time Line:
- Primary diagnosis and treatment
- Relapse and salvage therapy
- High-dose myeloablative therapy
- Marrow failure
- Disease remission
- Disease recurrence
- Continuous complete remission (cure)

CIBMTR

DMM00_A2.ppt
Cellular Therapy Course

- Multiple infusions along a period of time or single infusions, or implantation.
- Engraftment or not (depending on potency)
- Early toxicities
  - Infusion reactions
- Late toxicities:
  - Second malignancies (?)
  - “Miss-differentiation”
  - GVHD
  - Malignancy Relapse
- Milestones are not well defined for all cellular therapies.
Cellular Therapy Related to Hematopoietic Stem Cell Transplantation
HCT related Cellular Therapy: Donor Cellular infusions (DCI)

- DCI is a common terminology used in the CIBMTR forms.
- Related to any cell infusion occurring after a HCT without a preparative regimen
- The donor most times is the same, but it does not need to be.
  - “Off the shelf” MSCs: unknown donors
- Patients may receive GVHD prophylaxis.
Donor Cellular Infusion

Changing Chimerism

Complete Chimera
Indications for DCI

- Relapse prophylaxis
- Treatment of relapse: CML, AML, MM and others.
- Declining donor chimerism (graft failure)
- Treatment of post transplant malignancy:
  - PTLD (Lymphoma)
- Treatment of Viral Infections
- Treatment of GVHD (Mesenchymal Stromal Cells)
Lymphocyte Infusions post HCT

- T cells given as donor lymphocyte infusion after HSCT
- Antigen-specific T cells cultured from donor before infusion
- Antigen-specific T cells selected from donor and infused directly into recipient
Cytotoxic T-Cells (CTLs) for viral illness

- **Ummanipulated lymphocytes:**
  - Decrease numbers of viral specific CTLs
  - Presence of alloreactive T-cell that increase the risk of GVHD and further immunessupression.

- **Strategies:**
  - Decrease the content of alloreactive T cells;
  - Development of virus specific CTLs
    - EBV, Adenovirus and CMV.
Mesenchymal Stem Cells or Mesenchymal Stromal Cells (MSC)

- What are these cells?

- **Mesenchymal cells**: from embryology are cells from the mesenchima or mesoderm that will give origin to blood, blood vessels, bone and muscle.

- **Stromal cells**: cells from tissue stroma, promotes scaffolding and sustain other cells in the tissue.

- **Mesenchymal Stem cells**: cells from the bone marrow that have the capacity to generate bone, fat and cartilage.
Mesenchymal Stem Cells

- Cells with multipotent capacity,
- Demonstrate adherence to plastic
- Distinct immunophenotypic pattern.
- Bone marrow derived but similar cells are isolated from other tissues.

- **Multipotent mesenchymal stromal cells** is another terminology used in the literature and more appropriate for these cells.
MSCs in Clinical Medicine

- Simple isolation from bone marrow.
- Normal function is to protect and sustain hematopoietic stem cells.
- It does not require HLA matching.
- Currently being used for treatment of GVHD due to its effect in inducing immunetolerance.
- Other applications under investigation:
  - Promote engraftment in UCB HCT
  - Inflammatory bowel disease, autoimmune diseases, cardiac diseases.
Cellular Therapy for Regenerative Medicine or Emerging Indication
Cellular Therapy for Regenerative Medicine

- Rapidly evolving field with ramifications to most medical specialties
- Utilize cells for treatment of non-hematologic illnesses
- Bone marrow derived cells are most commonly used presently.
- Indications include: cardiovascular, neurological, autoimmune, musculoskeletal among others.
Cellular Therapy for Regenerative Medicine

(a) Catheter to heart
Lymphedema
Peripheral vascular disease

(b) Intracoronary injection
Adventitial delivery, cell grafting or ex vivo treatment of bypass grafts
Angioplasty
Intraventricular injection
Pericardial injection

(c) Intra-arterial delivery with or without angioplasty
Ex vivo transfection of vein grafts
Multiple intramuscular injections
Perivascular delivery
Cardiac Applications for Cellular therapies

- Indications with largest experience.
- Treatment for myocardial infarction.
- Mainly bone marrow derived cells:
  - Unmanipulated, CD34+ selection, MSC, cardiac progenitor cells.
- Infusion: intracoronary, intracardiac.
- Timing: within days from AMI but variable.
- Outcomes: Ejection fraction, other volume and pressure measurements, survival.
- Promising outcomes: improvement of EF and survival.
How does it work?

Regeneration of the ischemic myocardium

- angiogenesis
- arteriogenesis
- myocardial regeneration?
  - circulating stem cells?
  - resident stem cells?
  - Epicardium-derived cells (EPDC)?

Improvement of left ventricular ejection fraction
Cellular Therapy for Vascular Diseases

- Arterial insufficiency and ulcers.
- Cell types: bone marrow derived selected or unmanipulated.
  - Isolation of endothelial progenitor cells (EPCs)
- Intrarterial or intramuscular injections
- Improvement in ulcer healing, pain and arterial pressure indexes in the treated limb.
Therapeutic angiogenesis for patients with limb ischemia by autologous transplantation of bone-marrow cells

Cellular therapies for Autoimmune Diseases: MSCs in Scleroderma

Cellular Therapy for Neurologic Indications

- Parkinson’s disease, stroke, spinal cord injury, multiple sclerosis.
- Stereotactic implantation of cells
- MS: standard autologous HCT as salvage after high dose immunosuppression.
  - Use of MSC as an anti-inflammatory, remains investigational.
Cellular Therapy for Orthopedic Indications

- Improve of connective tissue healing.
- Application of tissue engineering with chondrocyte-layered matrices
- MSC derived chondrocytes
- Surgical implantation
Other indications being investigating

- Crohn’s Disease and ulcerative colitis
- Systemic Lupus Erythematosus
- Diabetes mellitus type I
- Rheumatoid Arthritis
- Avascular Necrosis of the Femur
- Amiotrophic Lateral Sclerosis
- Myasthenia gravis
- Acute cerebral vascular ischemia
- Bad mortgages!!!
Development of the Cellular Therapy Registry
Why a cellular therapy registry? Why should the CIBMTR be involved?

- HCT is a type of cellular therapy.
- Experience with HCT outcomes research.
- Experience in developing and maintaining large databases.
- Many cellular therapies are within the HCT field.
- Well established infrastructure
- Network of centers that are starting cellular therapy programs.
SCTOD

- Collect data on outcomes of all *allogeneic* hematopoietic stem cell transplants in the US
- Collect data on outcomes of all transplants facilitated by the CW Bill Young Program – even if transplant done outside the US
- **Include alternative uses of hematopoietic stem cells**
- Core set of data – sufficient to allow center-specific survival and other analyses
  - Subset of Report Form data
- Establish related donor-recipient specimen repository
Assessing potential risks

*Intramyocardium infusion of MSC in mouse and massive calcification in the injection site.*
Challenges

- Programs on cellular therapy are not the same as HCT, even though same institution.
- Beyond hematology and oncology fields.
- Other specialist might not be interested in collaboration.
- Clinical trials with confidential data.
- Off the shelf products with similar scrutiny as pharmaceutical products.
  - Cell types being patented.
Strategy

- Develop an interest group within the registry that became the Cellular Therapies Working Committee (CTWC)
- Establish a subcommittee to develop a data collection tool – CTED.
- Collaboration with European colleagues.
- Distribution and implementation of the form.
- Survey centers involved with cellular therapy.
Data Collection on Cellular Therapy
Data Collection on Cellular Therapies

- Incorporate data collection in the same system of CIBMTR forms.
- Separate data collection forms into:
  - HCT related → DCI
  - Cellular Therapies for regenerative medicine.
    - Any cell for any indication other than replacement of hematopoietic system.
HCT-related cellular therapy: DCI

- This data is already being collected.
- Registration level- Post-TED
- Research
  - DCI form → Baseline follow up form (Combine 2200)
- HCT vs DCI
  - Conditioning regimen
  - What was the previous transplant
  - Indication
  - Type of cells infused
## DCI in the Post-TED

<table>
<thead>
<tr>
<th>DONOR CELLULAR INFUSION (DCI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Date of first DCI:</strong> ____ __________ - ______ - ______</td>
</tr>
<tr>
<td><strong>Total # DCI in 10 weeks:</strong> ______</td>
</tr>
<tr>
<td><strong>Type of cell(s) (check all that apply):</strong></td>
</tr>
<tr>
<td>- Lymphocytes</td>
</tr>
<tr>
<td>- Fibroblasts</td>
</tr>
<tr>
<td>- Dendritic cells</td>
</tr>
<tr>
<td>- Mesenchymal</td>
</tr>
<tr>
<td>- Other, specify: ___________________</td>
</tr>
<tr>
<td><strong>Indication:</strong></td>
</tr>
<tr>
<td>- Planned</td>
</tr>
<tr>
<td>- Treat disease</td>
</tr>
<tr>
<td>- Treat PTLD, EBV-Lym</td>
</tr>
<tr>
<td>- Treat viral</td>
</tr>
<tr>
<td>- Treat GVHD</td>
</tr>
<tr>
<td>- Mixed Chimerism</td>
</tr>
<tr>
<td>- Loss/Decreased Chimerism</td>
</tr>
<tr>
<td>- Other, specify: ___________________</td>
</tr>
<tr>
<td><strong>Maximum Grade of Acute Graft Versus Host Disease (GVHD):</strong></td>
</tr>
<tr>
<td>- 0</td>
</tr>
<tr>
<td>- I</td>
</tr>
<tr>
<td>- II</td>
</tr>
<tr>
<td>- III</td>
</tr>
<tr>
<td>- IV</td>
</tr>
<tr>
<td>- Unknown</td>
</tr>
</tbody>
</table>

If another DCI was received in this reporting period, disease status before next DCI: **CR** □  **Not in CR** □  **Not assessed** □
Collection of DCI data in Research

- All DCIs within a 28 day period.
  - Additional DCIs beyond this period will require new reporting.
- Components:
  - Date
  - Number of infusions
  - Indication:
    - Planned, treatment of relapse, PTLD, GVHD, viral infection, stable/mixed chimerism, loss of chimerism, other.
Collection of DCI data in Research

- Components (Cont.):
  - Disease status (primary disease) and date.
  - Performance status
  - Cells source
  - Type of cells and cells doses
  - Cell manipulation
Collection of Cellular therapy for regenerative medicine

- Extremely broad topic.
- Registration-type form.
- Collaboration with the EBMT.
- Start as a non-longitudinal database.
- Assign an unique ID to all recipients.
- Trigger to collect the form may be applied different depending on the center.
# Cellular Therapy Essential Data - CTED

## CENTER IDENTIFICATION

- CIBMTR Center #: ___________  FBMTC Code (CIC) ___________
- Hospital: ____________________________
- Unit: [ ] Adult  [ ] Hematology  [ ] Oncology  [ ] Pediatric  
  [ ] Cardiovascular  [ ] Other ________________
- Contact person: ____________________________
- Phone #: ____________________________  Fax #: ____________________________
- Email: ____________________________
- Date of this Report: __________  YYYY  -  MM  -  DD

## RECIPIENT IDENTIFICATION

- Universal Recipient ID: ____________________________
- ID assigned by: [ ] CIBMTR  [ ] EBMT  [ ] Other ___________
- PACT Protocol #: ____________________________
- Gender: [ ] Male  [ ] Female
- Date of Birth: __________  YYYY  -  MM  -  DD

## INDICATION FOR TREATMENT

- Reason cellular therapy was performed:
  - [ ] New disease indication
  - [ ] Disease previously treated with Cellular Therapy
    - Specify indication:
      - [ ] Continuing treatment  [ ] Re-occurrence of the primary disease

If the patient required conditioning regimen prior to infusion of bone marrow derived cells—**STOP filling out this form and refer to the CTED manual for instructions.**
CTED: disease status, donor type and cell types

CELLULAR THERAPY
Status of primary disease at the time of cellular therapy:
- Acute disease
- Acute exacerbation of chronic disease
- Chronic disease

Source of donor cells:
- Autologous
- Allogeneic
  Specify:
  - Living donor
  - Cadaveric donor

Cellular product use:
- Single-patient use
- Multiple-patient use (cell lines)

Cellular product tissue source:
- Hematopoietic sources
  - Bone marrow
  - Cord blood
  - Peripheral blood
    Specify:
    - Mobilized product
    - Non-mobilized product

- Non-hematopoietic sources
  - Adipose tissue
  - Amniotic fluid
  - Cardiac tissue
  - Hepatic tissue
  - Neuronal tissue
  - Ophthalmic tissue
  - Pancreatic tissue
  - Placenta
  - Umbilical cord
  - Other source, specify
    - Adipose progenitor cells
    - Cardiac progenitor cells
    - CD34+ enriched cells
    - T-Lymphocyte

(Continued on next column)
CTED: Cell Manipulation and Clinical Participation

CELLULAR PRODUCT MANIPULATION

Manipulation of the cellular product performed:
☑ Yes  ☐ No  ☐ Unknown
   ➔ If yes, specify ex-vivo manipulation(s):
     ☐ Growth factor, specify ____________________________
     ☐ Cell selection, specify ___________________________
     ☐ Cell expansion, specify ___________________________
     ☐ Viral transfection, specify _________________________
     ☐ Non-viral transfection, specify _____________________
     ☐ Other manipulation, specify _______________________

CLINICAL STATUS OF PARTICIPATION

Recipient participation on clinical trial:
☑ Yes  ☐ No
   ➔ If yes, specify:
     ☐ Phase I
     ☐ Phase II
     ☐ Phase III
        ➔ Specify:
          ☐ Blinded  ☐ Randomized  ☐ Placebo controlled
     ☐ Single Institution
     ☐ Multi-center
CTED: Cellular Infusion

<table>
<thead>
<tr>
<th>Cellular Infusion Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route of cellular infusion:</td>
</tr>
<tr>
<td>- Intramuscular</td>
</tr>
<tr>
<td>- Intraperitoneal</td>
</tr>
<tr>
<td>- Intrartrial</td>
</tr>
<tr>
<td>Specify artery:</td>
</tr>
<tr>
<td>- Coronary</td>
</tr>
<tr>
<td>- Femoral</td>
</tr>
<tr>
<td>- Other artery, specify</td>
</tr>
<tr>
<td>- Intrathecal</td>
</tr>
<tr>
<td>- Intravenous</td>
</tr>
<tr>
<td>- Locally in the tissue</td>
</tr>
<tr>
<td>Specify local site:</td>
</tr>
<tr>
<td>- Heart</td>
</tr>
<tr>
<td>- Liver</td>
</tr>
<tr>
<td>- Bone</td>
</tr>
<tr>
<td>- Other site (organ/tissue), specify</td>
</tr>
<tr>
<td>- Other route, specify</td>
</tr>
</tbody>
</table>

Total number of cellular infusions administered in the period of 3 months from the first infusion: __________________________

Median number of cells infused per administration: _____ /kg /m² (circle one)

Total number of cells infused in the period of 3 months from the first infusion: __________________________ /kg /m² (circle one)

Another procedure performed associated w/cellular therapy (e.g., coronary artery bypass surgery, coronary stent placement, decompression of spinal cord injury, matrix implant)?
- Yes
- No
- Unknown
- If yes, specify procedure: __________________________

Did recipient experience any infusion reactions?
- Yes
- No
- Unknown
- If yes, specify severity:
  - Mild – transient reaction requiring no treatment or treatment with oral medication
  - Moderate – symptomatic reaction requiring parenteral medication
  - Severe – life-threatening or anaphylaxis
CTED: Disease indications

**CARDOVASCULAR DISEASES**

- Acute Myocardial Infarction
- Chronic Coronary Artery Disease (Ischemic, Cardiomyopathy)
- Heart Failure (Non-ischemic etiologies)
- Other CV indication, specify:__________________________
- Limb Ischemia
- Thromboangiitis obliterans
- Other Peripheral Vascular Disease indication, specify:__________________________

**Baseline (Prior to cellular therapy) Organ function parameters:**

- Ejection Fraction: ____________% measured by (circle one): 2D-Echocardiogram or MUGA or MRI
- Left Ventricular End-Diastolic volume: ____________mL
- Left Ventricular End-Systolic volume: ____________mL
- Number of previous infarcts:__________________________
- New York Heart Association Functional Classification (circle one): Class I or Class II or Class III or Class IV
- Canadian Cardiovascular Society Angina Classification (circle one): Class I or Class II or Class III or Class IV
- Mean Ankle-Brachial Pressure Index:__________________________
- Other Baseline Parameter, specify:__________________________

CIBMTR®
# CTED: Disease Indications

## Neurologic Diseases
- Acute Cerebral Vascular Ischemia
- Amiotrophic Lateral Sclerosis
- Multiple Sclerosis
- Myasthenia gravis
- Parkinson’s Disease
- Spinal Cord Injury
- Other Neurologic Disease indication, specify: ________________

## Musculoskeletal Diseases
- Avascular Necrosis of Femoral Head
- Osteoarthritis
- Osteogenesis Imperfecta
- Traumatic Joint Injury
- Other Musculoskeletal Disease indication, specify: ________________

## Autoimmune Diseases
- Rheumatoid Arthritis
- Systemic Lupus Erythematosus
- Systemic Sclerosis
- Diabetes Mellitus type 1
- Crohn’s Disease
- Ulcerative Colitis
- Other Autoimmune Disease indication, specify: ________________

## Other Diseases
- Wound Healing
- Other Disease indication, specify: ________________
CTED: Assessment of Response

RESPONSE TO CELLULAR THERAPY
Best clinical/biological response to cellular therapy?
- Complete response or normalization of organ function
- Partial response or partial normalization of organ function
- Any response, followed by disease progression
- No response
- Disease progression or worsening of organ function
- Unknown

Organ functioning for response agreement to cellular therapy (Laboratory Radiology or other)?
- Yes
- No
- Unknown

If yes, specify:
- Organ function parameter
- Response: Improved, Normalized, Unchanged, Worse

SURVIVAL
Recipient’s survival status at time of this report?
- Alive, specify date of most recent follow-up:
  
  Y Y Y Y - M M - D D

- Dead, specify: date of death:
  
  Y Y Y Y - M M - D D

  and main cause of death:
  - Disease relapse/progression/persistent disease
  - Related cell therapy
  - Other cause, specify
  - Unknown

- Lost to follow up, specify last known date alive:
  
  Y Y Y Y - M M - D

  Day of the month is estimated
Conclusions

- Definitions are important in this emerging field.
- Not all stem cells are the same, remember the concept of potency and self renewal.
- Rapidly changing field with a lot of promises with clinical data still maturing.
Conclusions

- Importance to set up an infrastructure for data collection for future studies.

- Applying our current forms system to this immense field will be a challenge but we have a good head start already!

Thank you
Cellular Therapy Working Committee

**Leadership:**
- **Armand Keating, MD**
  Princess Margaret Hospital, Toronto
- **Helen Heslop, MD**
  Baylor College of Medicine, Houston
- **Joshua Hare, MD**
  University of Miami, Miami

**Forms Subcommittee**
- Adrian Gee
- Sergio Giralt
- Helen Heslop
- Edwin Horwitz
- Armand Keating
- Diane Knutson
- Kathy Loper
- Marie Matlack
- Marcelo Pasquini
- Philip Rowlings

**Additional Input from EBMT:**
- Wim Fibbe
- Katarina LeBlanc
- Alan Tyndall
Q&A and Data Managers/Clinical Research Professionals Input