Cellular Therapy Registry
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Objective of CIBMTR Cellular Therapy Initiative

• To study therapies using cellular products for indications other than hematopoietic replacement or recovery.

• To provide an infrastructure to allow long-term follow-up of patients treated with cellular therapy products.
Cellular Therapy Registry
Implementation: Phases

- Exploratory Phase: who, where, what indication?
- Network Phase
- Database Development Phase
- Clinical Research

CIBMTR
Center for International Blood & Marrow Transplant Research
Transplant Center

Unique ID Form

1. Conditioning regimen
2. Intent to restore hematopoiesis

No

CTRM

Yes

Pre-TED

FormsNet
Cellular Therapies Registered with the CIBMTR – 2002 to 2014

- Number of infusions: 824
- Number of patients: 606
- Number of centers: 17
Cellular Therapies for Registered with the CIBMTR

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>606</td>
</tr>
<tr>
<td>Indication</td>
<td></td>
</tr>
<tr>
<td>Neurologic</td>
<td>467 (77)</td>
</tr>
<tr>
<td>Cardio and peripheral vascular</td>
<td>85 (14)</td>
</tr>
<tr>
<td>Autoimmune disease</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Musculoskeletal disease</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Other</td>
<td>50 (8)</td>
</tr>
<tr>
<td>ALL (CAR-Tcells)</td>
<td>30</td>
</tr>
<tr>
<td>Tissue source</td>
<td></td>
</tr>
<tr>
<td>Cord blood unit</td>
<td>467 (77)</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>86 (14)</td>
</tr>
<tr>
<td>Peripheral blood</td>
<td>37 (6)</td>
</tr>
<tr>
<td>Adipose tissue</td>
<td>4 (&lt;1)</td>
</tr>
<tr>
<td>Cardiac tissue</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Pancreatic tissue</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>T-lymphocyte</td>
<td>7 (1)</td>
</tr>
<tr>
<td>Missing</td>
<td>2 (&lt;1)</td>
</tr>
</tbody>
</table>
Hematopoietic Stem Cell Transplantation - Classification

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

- Myeloablative
- Reduced Intensity
- Non-myoablative

- Bone marrow
- Peripheral Blood
- Umbilical cord blood

- Negative or positive selection
- Ex vivo expansion
- In vivo selection
- Graft manipulation

- Conditioning Regimen Intensity
- Graft Source
Cellular Therapies - Classification

- **Autologous**
  - Allogeneic
  - Syngeneic

- **Tissue Specific**
  - Bone marrow
  - Peripheral blood

- **Unmanipulated**
  - Selected

- **Cells in solution**

- **Differentiated Stem cells**
  - Progenitor cells

- **Placenta**
  - Cord blood
  - Amniotic Fluid

- **Cardiac, Skin**, **Liver...**

- **Genetically modified**

- **Single vs. Donor Pool**

- **Live or cadaveric**

- **Donor**

- **Cell Type**
  - Genetic modified cells

- **Graft Source**
  - Tissue specific

- **Recipient preparation**

- **Infusion route**

- **HLA matching**

- **Graft manipulation**

- **Other Classifications**
HCT Model

Allogeneic HCT

- NMDP
- Cord Blood Banks
- HCT Center
- Longitudinal Data Reporting

Autologous HCT

- HCT Center
- Referring Center
- Longitudinal Data Reporting
CT Model

Manufacturers

Blood Banks

Cord Blood Banks

Cell Processing Lab

Industry

Center

FDA

Sponsor
Cellular Therapy Task Force - Objectives

• Build upon the existing infrastructure to develop a cellular therapy registry for research purposes

• Develop a cost-effective tool for long-term follow-up for cell therapy trials (centers, biotech, regulatory)

• Increase center participation in this initiative
Outline of the Registry

- Change the existing form 4000 from CTRM to CTED ("Cellular Therapy Essential Data Form")
- Trigger the pre-CTED whenever a cellular therapy is done, regardless of HCT
- Establish a follow-up structure for submission of post-CTED appropriate to each cellular therapy indication
- Create CRF forms for certain indications
- Develop an infrastructure to support collection and analysis of these data
CIBMTR Cellular Therapy Registry

• Prioritize certain indications for CRFs:
  – Malignancies (ALL, CLL and others)
  – Infections (Viral infections)

• Prioritize certain products for CRFs:
  – Genetically modified cells
    • Chimeric antigen receptors (CARs) for malignancy
    – Multi-virus-specific T-cells for infection

• But capture any cell therapy that is not a transplant
  – Including Donor Cellular Infusions (DCIs)
Model for the Cellular Therapy Registry

Cellular Therapy

- Pre-CTED
  - CRF
  - Comprehensive Data
  - Post CTED

Hematopoietic Cell Transplantation

- Pre-TED
  - CRF
  - Comprehensive Data
  - Post-TED

Form 2804/2814

Unique ID Assignment

Basic Level Of Data Collection

CRF
CTED Level Data – Applies to all Cellular Therapies

- **Pre-CTED**: demographic, indications, disease status prior to CT (if applicable) and therapy prior to CT.
- **Infusion form**: description of the product, information on manufacturing, product analysis and infusion details.
- **Post-CTED**: follow-up infusions, recipient survival and disease status, cause of death, development of malignancies, persistence of the product, development of CRS.
Basic Model for Collection of all Cellular Therapies

For All Planned Infusions

Pre-CTED 4000

Infusion Form 4006

For All Planned Infusions

Post-CTED 4100

New Infusions 4006

For All Infusions Given: since the last form

3m, 6m, 1y and yearly thereafter
CRF Level Data for Cellular Therapies

• Data collected:
  – Disease information and follow-up
  – Infection information and follow-up
  – HLA typing and matching (if applicable)
  – Make use of forms already in existence for HCT

• Case selection:
  – Based on the indication and the cell product utilized
Model for Collection of Cellular Therapy for Hematologic Malignancies

Pre-CTED
- Disease Forms
- Infusion Form

Post-CTED
- Disease F/U
- New Infusions

For All Planned Infusions
- For All Planned Infusions

For All Infusions Given: *since the last form*

3m, 6m, 1y and yearly thereafter
Model for Collection of Cellular Therapy for Infection

- Pre-CTED
  - Infection Form
  - Infusion Form
  - HLA Form
    - For All Planned Infusions

- Post-CTED
  - Infection F/U
    - For Allogeneic Products
  - New Infusions
  - HLA Form
    - For All Infusions Given: since the last form

3m, 6m, 1y and yearly thereafter
Should all Follow-up be the Same?

• Follow-up will vary according to the type and indication of cellular therapy:
  – Genetically modified cells for any indication
  – Unmanipulated donor lymphocyte infusion after HCT for treatment of infection
  – MSC infusions for treatment of GVHD
  – Third party CTLs

• Example: FDA mandates 15-year follow-up after the infusion of genetic modified cells.
How to Define a Cell Product? Example CD19-CAR

- **Donor**: Autologous
- **Tissue Source**: Peripheral Blood
- **Cell Type**: Lymphocytes: CD8+ cells

**Specific Commercially Available Product**

- Capture the name of the product
- **Product ID**
- **Clinicaltrials.gov Number for the Protocol**
Cellular Therapy Scenarios

- Several scenarios for which we need to collect data
  - Cellular therapy only
    - Regenerative medicine
    - CAR T-cells for malignancy
    - CTL for infection
  - Co-infusions: HCT plus cellular therapy
  - Sequential cellular therapies for same/different indications
  - Cellular therapy followed by HCT (e.g. bridge to HCT)
  - HCT followed by cellular therapy (e.g. DCI)
Several scenarios for which we need to collect data

- Cellular therapy followed by HCT (e.g. bridge to HCT)
- Cellular therapy to cellular therapy (new indication)
- Co-infusions: HCT plus cellular therapy
- HCT followed by cellular therapy (e.g. DCI)
- Cellular therapy only

- Regenerative medicine
- CAR T-cells
- CTL for infection

Required
Optional
Data Collection Approach

• Reimbursement similar to HCT
• Pilot data collection at different centers in patients receiving diverse products for diverse indications

• Data collection at centers:
  – Important to include cell processing laboratory;
  – Multiple programs (including HCT program) at a single center

• Implement Data Back to Centers functionality for CT
Important Issues to Address in Establishing a Mechanism for Long-term Follow-up of Cellular Therapy

• Ability to capture all patients of interest
• Ability to capture all variables of interest
• Ensuring data quality
• Maintaining long-term follow-up
• Ensuring confidentiality, security and regulatory compliance
• Making data rapidly available for multiple users / uses
• Cost-effectiveness
Important Issues to Address in Establishing a Mechanism for Long-term Follow-up of Cellular Therapy

• Similar to the issues that have been tackled by the BMT community for the past 40+ years
• Effectively addressed by large multi-center, multi-national outcomes registries/research networks dealing with:
  – Similar patient population
  – Interventions with similar issues
• Data accumulated has been used effectively to advance the field
• Represents cost-effective approach since much of the infrastructure already exists
Additional Issue to be Addressed for Cellular Therapy: Proprietary Data

- Projects under IND / IDE or pharmaceutical cell products
- Data collection will be the same
- Establish embargo plan that would control release of outcome data until agreed upon milestone
- These plans will be protocol or project specific
Funding

• Infrastructure development, even though it takes advantage of existing systems, is expensive

• Submitting application for administrative supplement to U24
  – Will ask for additional funding in next competitive renewal

• Discussions with several companies
  – Novartis discussions most advanced
Cellular Therapy Registry Status

• CTED level forms are completed and are designed
• Release in FormsNet planned for Summer 2016
• CRF level forms under development
• Next steps:
  – Harmonization with EBMT
  – Develop a protocol for collection of long-term follow-up data for genetically modified cells