Challenges in Capturing Long Term Follow up of Recipients of Genetically Modified Cells

Cell Therapy Liaison Meeting
January, 2018
Outline

• Development of the Cellular Therapy Registry
  – Standardized Data Collection Platform
  – Data Standards and Sharing
  – Considerations for capturing long term follow up.
• Recommendation vs. Interpretation for Commercial Genetic Modified Products.
• Approaches to optimize follow up.
• Overview and recommendations.
A Little History: We Have Been Around for a Very Long Time

- 1968: First successful HCTs
- 1971: National Marrow Donor Program established
- 1974: International Bone Marrow Transplant Registry established
- 1988: CIBMTR established

Graph showing the increase in transplants from 1968 to 2013, with labels indicating significant events.
The CIBMTR is a research collaboration between NMDP/Be The Match and the Medical College of Wisconsin.
Characteristics of HCT Registry Data

• Population-based
  – Population defined by receipt of a specific type of therapy
  – No other eligibility criteria (i.e. do not need to be in a specific clinical trial or in a certain kind of center)
  – Requirement for consecutive reporting

• Longitudinal
  – No specific end date for follow-up
  – Depends on ability of treating physician/center to maintain contact

• Variable dataset
C.W. Bill Young Cell Transplantation Program*

**US Department of Health and Human Services**

**Advisory Council on Blood Stem Cell Transplantation**

**HRSA/Division of Transplantation**

- National Cord Blood Inventory
  - Individually contracted and accredited cord blood banks

- Cord Blood Coordinating Center

- Bone Marrow Coordinating Center

- Stem Cell Therapeutic Outcomes Database

- Office of Patient Advocacy/Single Point of Access
  - Public Interface

**Components of the C. W. Bill Young Cell Transplantation Program**

- Transplant centers, patients and families
- Referring physicians

Made reporting allogeneic transplant data *mandatory* in the US in 2005

* Created by the Stem Cell Therapeutic and Research Act of 2005 and the Stem Cell Therapeutic and Research Reauthorization Act of 2010

**CIBMTR**

CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

---

Assembly12_41.ppt
Requirements of SCTOD

• Collect data
  – Outcomes of allogeneic HCTs performed in the US or performed outside the US with US grafts
  – Other therapeutic applications of blood stem cells
    • Regenerative medicine
    • Cellular therapy of malignant disease
  – Quality of life

• Disseminate data
  – Multiple Users, Formats

• Analyze data
  – Center-specific outcomes
  – Wide Range of Research

• Research Repository
CIBMTR Cellular Therapy Initiative - Objectives

• 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 genetically manipulated cellular therapy products.
CIBMTR Cellular Therapy Initiatives - History

• **1990s-Jan 2017**: Donor lymphocyte infusions to treat post-transplant relapse/infection capture on HCT forms

• **2006- June 2016**: SCTOD mandate to collection data on non-HCT uses of blood stem cells
  – Outreach to disease specialist
  – Simple registry of activity

• **July 2016-current**: Revamp the Cellular Therapy Registry with the launch of CTED forms.
  – Expanded fields on indications, product manufacturing and complications, **long term follow up mechanism**
  – Converge all cellular therapies, including DCIs in one track.
  – NCI Pilot Project
CIBMTR Cellular Therapy Initiatives - History

- **1990s-Jan 2017**: Donor lymphocyte infusions to treat post-transplant relapse/infection capture on HCT forms
- **2006- June 2016**: SCTOD mandate to collection data on non-HCT uses of blood stem cells
  - Outreach to disease specialist
  - Simple registry of activity
- **July 2016-current**: Revamp the Cellular Therapy Registry with the launch of CTED forms.
  - Expanded fields on indications, product manufacturing and complications, **long term follow up mechanism**
  - Converge all cellular therapies, including DCIs in one track.
  - NCI Pilot Project
CIBMTR Cellular Therapy Initiatives - History

• **2014-2017**: active initiative to understand the community’s needs and to develop an infrastructure to meet those needs
  – CIBMTR Advisory Committee/Advisory Council presentations
  – Forum of wide range of stakeholders in 2015, 2016 and 2017
  – Series of meetings with industry and international registries

• Summer 2016: new Cellular Therapy Registry forms launched in FormsNet
CTED Pilot

• NCI-funded 1 year project to “Beta” test the CTED forms.
• Launched in July 2016
• Direct input from centers at two in person meetings
• Data harmonization and input from international partners (EBMT and JHSCT)
• Input resulted in the release of revised forms July 2017.
• Time studies are ongoing to determine reporting burden and appropriate reimbursement rates
Data Flow – Transplant

Non-US; US Auto
Voluntary

US Related*; Unrelated**
Mandatory in US (since 2007)

Transplant Essential Data Form

Comprehensive Report Forms
Voluntary

Single CIBMTR Database (Research Database)

*Donor outcomes routinely collected
**Donor outcomes collected on subset
Data Flow – Cellular Therapy

Non-HCT Cellular Therapy

Cellular Therapy Essential Data Form + Disease-specific CRF

Supplemental Report Forms

Single CIBMTR Database (Research Database)
Integrated Data Flow

Cellular Therapy

Pre-CTED

Post CTED

CRF

Supplemental Data

Hematopoietic Cell Transplantation

Pre-TED

Post-TED

Form 2804/2814

Unique ID Assignment

Comprehensive Data

CRF

Supplemental Data

Data
Cellular Therapy Registry Data Flow

- **Unique ID Assignment and Indication F2804/2814**
- **Pre-CTED F400**
  - Disease Classification F2402
  - Indications for CT
  - Product F4003
    - Product information and details on manufacturing
  - Post-CTED F4100
  - Outcomes form
- **Infusion F4006**
  - Infusion details, route and cell doses.
- **Subsequent Neoplasm F3500**
  - Event-driven form
- **Disease specific insert**
  - Disease characteristics, prior treatment and condition prior to CT. For example: acute leukemia and NHL.
  - Disease response and subsequent treatments
  - 3, 6 and 12 months then yearly
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 Specific Data

• Treatment description
  – Lymphodepleting chemotherapy and adjuvant treatment (e.g. immune checkpoint inhibitor)

• Cytokine Release Syndrome:
  – Capture all signs and symptoms to adapt to any grading system.
  – Treatment and resolution

• Other important outcomes
  – Neurotoxicities, other toxicities, infections, hypogammaglobulinemia, cytopenias, GVHD, subsequent neoplasms, death.

• Persistence of cell product.
Indications for Cellular Therapy, 2016-2017 – CTED Pilot (N=475)
**Cellular Therapies for Treatment of Malignancies – Excluding DLI – July 16’ to November 17’**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N=149</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Centers</strong></td>
<td>50</td>
</tr>
<tr>
<td><strong>Indication</strong></td>
<td></td>
</tr>
<tr>
<td>Acute Lymphocytic Leukemia</td>
<td>62</td>
</tr>
<tr>
<td>Acute Myeloid Leukemia</td>
<td>2</td>
</tr>
<tr>
<td>Hodgkin Disease</td>
<td>6</td>
</tr>
<tr>
<td>Multiple Myeloma</td>
<td>10</td>
</tr>
<tr>
<td>Non Hodgkin Lymphoma</td>
<td>61</td>
</tr>
<tr>
<td>Other Hematologic Malignancy</td>
<td>2</td>
</tr>
<tr>
<td>Solid Tumors¹</td>
<td>6</td>
</tr>
<tr>
<td><strong>Genetically Modified Cells²</strong></td>
<td>114</td>
</tr>
</tbody>
</table>

¹ GBM, Neuroblastoma and Sarcoma ² CAR: BCMA, CD19, CD22, CD30, CD16v, CD123 and CD171; Ny1-ESO.
Data Processing, Quality and Sharing

CIBMTR Integrated Data Warehouse (IDW)

Data Sources
- FN
- Laboratory EHR
- Other Ops Systems

Operational Data Store
- ETL

Integrated Data Store
- ETL

Unified Domain
- ETL

Data Quality Assessments

Analytical Data Marts
- Metadata Mart
- CT Mart
- HCT Mart
- Data Quality Mart
- Other Marts...

Data Products & Outputs
- Reports
- Dashboards
- eDBTC
- Data Extracts
- Analytics
- APIs
- Applications
- Other

CT & HCT Center Data Quality Applications

Cancer Data Ecosystem Federated Repositories & Applications
eDBtC Patient Level Data
## Follow up Structure

<table>
<thead>
<tr>
<th>Type of cells</th>
<th>Time points</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCT</td>
<td>3m, 6m, 1 year, yearly up to 5 years then every 2 years</td>
<td>Until death</td>
</tr>
<tr>
<td>Genetically Modified Cells</td>
<td>3m, 6m, 1 year, yearly</td>
<td>15y</td>
</tr>
<tr>
<td>Third Party CTLs</td>
<td>3m, 6m, 1 year, yearly</td>
<td>2y then HCT</td>
</tr>
<tr>
<td>Unmanipulated donor lymphocyte infusions</td>
<td>3 m</td>
<td>HCT</td>
</tr>
<tr>
<td>Mesenchymal stem cells</td>
<td>3 m</td>
<td>HCT</td>
</tr>
</tbody>
</table>
Issues Pertinent to Cellular Therapy Follow-up – Multiple treatments and centers

• Consider Jane Doe:
  – 12 year with early relapse of ALL
  – CAR-T-cell therapy #1 – no response
  – CAR-T-cell therapy #2 – different construct, different institution - response
  – HCT – third institution
    • *Viral-specific T-cell therapy post-transplant*

• Who reports what to where? How does the data flow?
CT Model for Long Term Follow up

Center 1

Sponsor

Cellular Product 1

Patient

Center 2

Sponsor

Cellular Product 2

FDA

eDBTC

eDBCT=Enhanced Data Back to Centers
Issues Pertinent to Cellular Therapy Follow-up – 15 years

- Optimize follow up and patient tracking through ePRO.
- Patients consent to allow the CIBMTR to directly contact them.
- Dedicated coordinator group responsible to communicate with patients.
- Data from this mechanism would be available to centers through eDBtC similar to clinical data.
Issues Pertinent to Cellular Therapy Follow-up – Pregnancy

• Outcome forms capture pregnancies after CT and outcomes.
• Capture information of health of the baby is challenging.
  – Rely on center to report
  – Direct patient contact
  – Request for pediatricians’ notes and growth charts through the ePRO system.
Commercial CAR-T cell: Current Status

CTED
Modifications:
• Additional supplemental data
• Follow up every 6 months for 15 years

Recommendations

CTED with same schedule Modifications:
• Mechanism to collect samples from patients who develop subsequent neoplasms
Conclusions and Recommendations

• Standardized database will be important to the field.
  – Minimal set of data elements required;
  – Avoid having multiple databases for each company and for similar cellular products.

• Recommendation of minimal follow up schedule to avoid increasing the burden of data collection and maximizing efficiency.

• Promote innovative approaches for patient tracking and follow up.