Regulatory Challenges in Apheresis
Global Perspectives - Cell Therapy

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Objectives

1. Describe the different global cell therapy standards
2. Can we align those standards?
3. How can we comply with cell therapy standards – case scenarios
# Cell Therapy Standards

<table>
<thead>
<tr>
<th>Organization</th>
<th>Accreditation Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>AABB</td>
<td>Two years</td>
</tr>
<tr>
<td>FACT</td>
<td>Three years</td>
</tr>
<tr>
<td>JACIE</td>
<td>Four years</td>
</tr>
<tr>
<td>FDA</td>
<td>Interval not set</td>
</tr>
<tr>
<td>WMDA</td>
<td>Five years</td>
</tr>
</tbody>
</table>
JACIE Accredited Facilities
Worldwide Location of Unrelated Donor Registries

Petersdorf EW, BMT, 45, 807–8 (2010)
• WMDA fosters international collaboration to facilitate the exchange of high quality haematopoietic stem cells for clinical transplantation worldwide and to promote the interests of donors.

- Global standards cover all aspects of unrelated hematopoietic stem cell cell registry operations.
• NMDP Standards set forth basic guidelines and requirements for programs working with the NMDP.
• Standards encompass network participation criteria with requirements for transplant hospitals, recruitment centers, product collection centers, etc.
• Standards for the donation process; product collection, storage, transportation, processing and labeling; adverse events, complaints and non-conforming products.
Can We Align It All Together?
AHCTA mission statement:

…the above named organizations commit themselves to the harmonization of their respective standards with the objective of creating a single set of quality, safety and professional requirements for cellular therapy…
Comparison of Donor Standards
The tables are populated with data from the FACT-JACIE, Netcord-FACT, WMDA and AABB Standards

<table>
<thead>
<tr>
<th>Definitions</th>
<th>Abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>WMDA International Standards for Unrelated Hematopoietic Stem Cell Donor Registries Version 2014</td>
<td>W</td>
</tr>
<tr>
<td>FACT-JACIE International Standards for Cellular Therapy Product Collection, Processing and Administration5th Edition</td>
<td>F-J</td>
</tr>
<tr>
<td>Netcord-FACT International Standards for Cord Blood Collection, Banking and Release for Administration5th Edition</td>
<td>NC-F</td>
</tr>
<tr>
<td>AABB Standards for Cellular Therapy Services 6th Edition</td>
<td>AA</td>
</tr>
<tr>
<td>Cord Blood Bank</td>
<td>CBB</td>
</tr>
<tr>
<td>Requirement is addressed in standards</td>
<td>X</td>
</tr>
<tr>
<td>Requirement is not addressed in standards</td>
<td>-</td>
</tr>
<tr>
<td>REQUIREMENTS</td>
<td>W</td>
</tr>
<tr>
<td>------------------------------------------------------------------------------</td>
<td>----</td>
</tr>
<tr>
<td>consequences of not donating to the potential recipient</td>
<td></td>
</tr>
<tr>
<td>Obtained by licensed physician or other health care provider familiar with the</td>
<td>X</td>
</tr>
<tr>
<td>collection procedure</td>
<td></td>
</tr>
<tr>
<td>Minor consent obtained from parents or legal guardian according to applicable</td>
<td>X</td>
</tr>
<tr>
<td>laws and regulations</td>
<td></td>
</tr>
<tr>
<td>Consent and authorization from donor in advance to releasing health</td>
<td></td>
</tr>
<tr>
<td>information to transplant physician and recipient as appropriate</td>
<td></td>
</tr>
<tr>
<td>Provision of documentation of consent to collection staff prior to the</td>
<td>X</td>
</tr>
<tr>
<td>collection procedure</td>
<td></td>
</tr>
<tr>
<td>Mother donating cord blood informed to contact CBB if infant donor develops</td>
<td></td>
</tr>
<tr>
<td>serious disease post donation</td>
<td>-</td>
</tr>
<tr>
<td>Donor Suitability Requirements</td>
<td></td>
</tr>
<tr>
<td>Established criteria and evaluation procedures to protect the safety of the</td>
<td>X</td>
</tr>
<tr>
<td>donor</td>
<td></td>
</tr>
<tr>
<td>Abnormal findings during workup reported to prospective donor with</td>
<td></td>
</tr>
<tr>
<td>recommendations for follow-up care</td>
<td></td>
</tr>
<tr>
<td>Evaluation to include potential risks of the collection procedure.</td>
<td></td>
</tr>
<tr>
<td>Potential risks shall include where relevant:</td>
<td></td>
</tr>
<tr>
<td>Possible need for venous access</td>
<td>X</td>
</tr>
<tr>
<td>Mobilization</td>
<td>X</td>
</tr>
<tr>
<td>Anesthesia</td>
<td>X</td>
</tr>
<tr>
<td>Donor Evaluation for Transmissible Disease (Eligibility)</td>
<td></td>
</tr>
<tr>
<td>Procedures in place for evaluation of risk of disease transmission from donor</td>
<td>X</td>
</tr>
<tr>
<td>products</td>
<td></td>
</tr>
</tbody>
</table>

Donor standards version Dec 13-2013
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Case 1 – Healthy Allo Donor

• 8 yo HLA-matched sibling donor, sickle trait
• PMH: Non significant
• Physical Exam: No major concerns
• Plan: G-CSF 10 µg/kg/d; HPC collections by Apheresis on day 4&5 of G-CSF

? Considerations for G-CSF & Apheresis ?
Standard (1)


  *living allogeneic and autologous donors shall be evaluated for the risk of hemoglobinopathy before the administration of G-CSF*

Rationale behind?

<table>
<thead>
<tr>
<th>REQUIREMENTS</th>
<th>W</th>
<th>F-J</th>
<th>NC-F</th>
<th>AA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factors evaluated by medical history, physical examination, examination of relevant medical records, and laboratory testing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evaluation of risk of hemoglobinopathy</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
SDF-1/CXCL12, secreted by BM stromal cells, binds to CXCR4 ligand, expressed on CD34+ HPCs
G-CSF Induced Mobilization

From Lapidot and Petit, Experimental Hematology 2002;30:973-981
Mechanism of Action for Mobilization

G-CSF Vs. AMD3100 (Mozobil)

G-CSF Complications in Sickle Cell Disease

- G-CSF can cause vaso-occlusive crisis with in pts with Hgb S/S, S/C or S/β thal

- 11 case reports of G-CSF use in SCD. 7 require hospitalization, while 4 others experienced no complications

- Multi-organ failure & death in one previously asymptomatic 47 yo donor with Hgb S/C

- Crises might be related to acute ↑ PMN and PMN activation

References:

Are Donors With Sickle Trait (Hb AS) at Increased Risk from G-CSF?

- Donors with sickle trait were safely mobilized and collected.
- The sickle trait donors did have higher symptom score than control donors.
- There were no symptoms suggestive of sickle crisis.
- No difference in CD34 yield or in apheresis and processing procedures.
- The risk is limited.

Kang et al, Blood 2002;99:850
FACT/AABB Standards: living allogeneic and autologous donors shall be evaluated for the risk of hemoglobinopathy before the administration of G-CSF.

There shall be written documentation of an interim assessment of donor suitability for the collection procedure performed by a qualified person immediately prior to each collection procedure.

Rationale behind?
Case 2

• You are evaluating a 45 yo donor who is to donate G-CSF -Mobilized PBSC for her HLA matched sibling with AML.
• She already had 5 days of G-CSF and is about to start the collection
• Complaints of new abdominal pain with radiation to the left shoulder

What are the concerns for this donor?
G-CSF and The Spleen

**Splenic Enlargement:**
- Spleen size has been studied in over 100 healthy HPC, Apheresis donors
- In almost all donors: spleen volume and length increases 10-13% on average
- Begins to reverse quickly with a return to baseline within 10 days after completion of G-CSF
- Due to extramedullary hematopoiesis
- 🚨🚨 donor risk for splenic rupture

Stroncek et al, Transfusion 2003;43:609  Platzbecker et al, Transfusion 2001;41:184
G-CSF and The Spleen

Splenic Rupture:

- 11 cases of Splenic rupture reported to date in adult donors of HPC, Apheresis\(^1\) (5 auto, 6 allo donors)
- The incidence is estimated to be 1:5,000 - 1:10,000\(^2\)
- Splenic rupture has not been reported in children
- Histologic examination of the ruptured spleen: massive extramedullary hematopoiesis & subcapsular bleeding

\(^1\)Bone Marrow Transplant 2007;40:361  \(^2\)Pediatr Blood Cancer 2006;46:422
Splenic Rupture

Common signs and symptoms:

- Nausea, malaise
- Pain radiating to left shoulder
- ↓ Blood Pressure
- ↓ Hematocrit

- Can happen anytime after initiation of G-CSF
  - most common between D5-10

Dincer et al. J Ped Hematol Oncol 2004; 26:761
Additional Serious Adverse Events Related to G-CSF

- **Vascular events**: MI, increase anginal episodes, CVA
- **Flare of autoimmune disease**: RA, AS, SLE, MS, Scleroderma, thyroid dysfunction (preexisting Antithyroid Abs)
- **Eye inflammatory responses**: keratitis, episcleritis, iritis

- Careful screening of history
- Risk versus benefit
- Interim assessment of complaints

Bone Marrow Transplantation 2007;39:577  JCA 2006;21:116
FACT Standard **C8.5** & AABB standard **5.13.1**: There shall be written documentation of an interim assessment of donor suitability for the collection procedure performed by a qualified person immediately prior to each collection procedure.
Standard (3)

  - A complete blood count, including platelet count, shall be performed within 24 hours prior to each HPC collection by apheresis.

**C8.5.2:** There shall be peripheral blood count criteria to proceed with collection.

*Rationale behind?*
Case 3: Platelets & HPC, Apheresis collection

- 29 yo healthy male sibling donor mobilized with G-CSF 10 µg/kg/d
- Apheresis d4 G-CSF: 12 L; heparin + ACD-A → temp 40°C at procedure end; hospitalized
- Collection yield: 4.5 x 10^6 CD34+ cells/kg
- Fever resolved; no source identified
- F/U apheresis d10 after 1st collection for DLI: severe platelet clumping noted → abort
Post Collection Donor Issues

Platelets

- Each collection, a donor loses \( \sim 4 \times 10^{11} \) plt
- G-CSF can cause ↓ Plt count (usually mild)
- After one collection: Plt count ↓ \( \sim 30\% \)

**Table 2** Changes in peripheral blood cell counts during G-CSF administration and after apheresis session

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>basal</td>
<td>day 5</td>
<td>post apheresis</td>
</tr>
<tr>
<td>WBC</td>
<td>5.5 (3.9–12.3)</td>
<td>56 (37–75)*</td>
<td>—</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>1.9 (1.7–4.3)</td>
<td>4.4 (2.1–14.6)*</td>
<td>—</td>
</tr>
<tr>
<td>Platelets</td>
<td>228 (161–286)*</td>
<td>207 (155–328)*</td>
<td>137 (96–198)</td>
</tr>
</tbody>
</table>

Hematology Am Soc Hematol Educ Program 2005:469
Platelets loss – Autologous Collections

Platelets loss – Allogeneic Collections

Post Collection Donor Issues Platelets (cont.)

- After 2 collections, plt <100,000 in 20-23% of donors
- Delayed plt recovery: start to rise only $\geq 2$ days; return to baseline 7-10 days post collection
- Donors with low platelet counts are at potential risk from bleeding and remain at risk for up to 1 week
- Always consider other/additional cause e.g. Heparin Induced Thrombocytopenia

Being Compliant w/the Standard (3)

- FACT standard C8.5.1 & AABB 5.12.4:
  
  A CBC, including platelet count, shall be performed within 24 hours prior to each HPC collection by apheresis.

- C8.5.2: There shall be peripheral blood count criteria to proceed with collection.
Conclusions

• Cellular therapy standards ensure high quality products
  - standardize processes related to collection, processing & administration

• The different sets of the standards have similarities
  - Based on scientific literature, clinical practice and regulations

• Understanding the rationale behind the standards can help with compliance
Thank you!