T-A G-v-H D Market Trends: Gamma to X-ray to Pathogen Inactivation

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With thanks to Susan Leitman, MD, Dept. of Transfusion Medicine, NIH, Bethesda, MD
Conflicts of interest (financial)

- PacifiCord: Medical Director
- ISP (now Ashland Specialty Ingredients): Consultant
- Chiron/Novartis: Consultant
61 year old woman with chronic lymphocytic leukemia (CLL)

- Many courses of chemotherapy over years (including fludarabine)
- Autologous PBSC transplant as part of experimental protocol – discharged
- Admitted to community hospital with fever, pancytopenia
- Transfused with 1 packed RBC and 3
3 days later, onset of fever and rash

Admitted to university hospital where PBSC transplant was performed

Consultation by Hem/Onc Fellow who recently completed rotation at regional blood centers
<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient pre Tx</strong></td>
<td>1, 2</td>
<td>44, 60</td>
<td>11, 13</td>
</tr>
<tr>
<td><strong>Patient post Tx</strong></td>
<td>2</td>
<td>18, 60</td>
<td>3, 8, 11, 13</td>
</tr>
<tr>
<td><strong>Implicated Donor RBCs</strong></td>
<td>2</td>
<td>18, 60</td>
<td>3, 8</td>
</tr>
<tr>
<td><strong>Other Donor platelets</strong></td>
<td>2, 24</td>
<td>35, 51</td>
<td></td>
</tr>
<tr>
<td><strong>Other Donor platelets</strong></td>
<td>1, 26</td>
<td>8, 60</td>
<td>1, 3</td>
</tr>
<tr>
<td><strong>Other Donor platelets</strong></td>
<td>3, 30</td>
<td>35, 49</td>
<td>1, 13</td>
</tr>
</tbody>
</table>
Transfusion-Associated Graft versus Host Disease

- Rare but devastating complication of transfusion
- Mediated by immunocompetent transfused T-lymphocytes, which engraft, proliferate, and mount a severe immune reaction targeted against the HLA antigens of the host
- Host may be:
  - (1) severely immunocompromised
Patients at Risk of TA-GVHD

- Recipients of intrauterine transfusions (fetus)
- Recipients of postnatal exchange transfusions (neonates, HDN)
- Infants & children with severe congenital immunodeficiency states (SCID, WAS)
- Hematopoietic transplant recipients (allogeneic, autologous)
- Patients with hematologic malignancies (lymphoma, leukemia)
- Patients with solid tumors
- Patients receiving purine analogues
  - Fludarabine, cladribine, pentostatin
- Recipients of HLA-homozygous, haploidentical blood
### Key distinguishing features of acute G-v-H D after transfusion and after stem cell transplantation (SCT)

<table>
<thead>
<tr>
<th></th>
<th>Transfusion</th>
<th>SCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>0.1 – 1.0%</td>
<td>30 – 70%</td>
</tr>
<tr>
<td>Onset</td>
<td>2 – 47 days</td>
<td>35 – 70 days</td>
</tr>
<tr>
<td>Pancytopenia</td>
<td><strong>Frequent</strong></td>
<td>Rare</td>
</tr>
<tr>
<td>Bone marrow</td>
<td><strong>Hypocellular</strong></td>
<td>Not affected</td>
</tr>
<tr>
<td>Duration</td>
<td>&lt;54 days</td>
<td>Months</td>
</tr>
</tbody>
</table>
Frequency of Transfusion From HLA Homozygous Donor to Recipient Heterozygous for that Haplotype Among Different Populations

<table>
<thead>
<tr>
<th>Population</th>
<th>Parent/Child</th>
<th>Sibling</th>
<th>Unrelated</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Whites</td>
<td>1:475</td>
<td>1:902</td>
<td>1:7174</td>
</tr>
<tr>
<td>Japanese</td>
<td>1:102</td>
<td>1:193</td>
<td>1:874</td>
</tr>
<tr>
<td>Canadian Whites</td>
<td>1:154</td>
<td>1:294</td>
<td>1:1664</td>
</tr>
<tr>
<td>Germans</td>
<td>1:220</td>
<td>1:424</td>
<td>1:3144</td>
</tr>
<tr>
<td>Koreans</td>
<td>1:183</td>
<td>1:356</td>
<td>1:3220</td>
</tr>
<tr>
<td>Spanish</td>
<td>1:226</td>
<td>1:438</td>
<td>1:3552</td>
</tr>
<tr>
<td>Italian</td>
<td>1:434</td>
<td>1:854</td>
<td>1:12870</td>
</tr>
</tbody>
</table>
Paling Risk Scale for Major Transfusion Hazards

10^8 | 10^7 | 10^6 | 10^5 | 10^4 | 10^3 | 10^2 | 10^1 | 10^0

West Nile

HIV
HCV
HBV
Bacteria
TRALI
TA-GVHD
Mis-Transfusion

Selected patient groups

Metabolic risk in neonates

Cardiac toxicity
Preventing T-A G-v-H D

- Leukocyte Reduction – reduces but doesn’t eliminate risk
- Pathogen Inactivation/reduction using photochemistry - YES
- Irradiation (gamma or X-ray) – YES
Williamson LM et al. The impact of universal leukodepletion of the blood supply on hemovigilance reports of posttransfusion purpura and transfusion-associated graft-versus-host disease.

Transfusion. 2007;47:1455-67
## Universal leukodepletion (LD) pre PTP and T-A G-v-H D

<table>
<thead>
<tr>
<th></th>
<th>Pre LD</th>
<th>Post LD</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTP</td>
<td>10.3/yr*</td>
<td>2.3/yr**</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>T-A G-v-H D</td>
<td>11</td>
<td>2</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

* 1/31 (3%) received platelets
Photochemistry treatment of blood = chemical + light (UV)

- Crosslinking of DNA or RNA in microbes = pathogen inactivation (PI)
- Crosslinking of DNA in leukocytes = prevention of G-v-H D following a transfusion
Pathogen inactivation as an alternative to current TA-GvHD safeguards

- Gamma irradiation can inactivate residual donor leukocytes if administered in sufficient dosage (2,500 cGy)$^1$
  - TA-GvHD reported after gamma irradiation with 2,000 cGy$^2$
  - Protection relies upon identifying those patients who are at risk, so gamma-irradiated units can be provided
Pathogen inactivation as an alternative to current TA-GvHD safeguards

- Treatment with the INTERCEPT Blood System can inactivate donor leukocytes completely even if administered in a dose 3000-fold smaller than nominal
  - Treatment with the INTERCEPT Blood System not only prevents leukocyte replication, but also inhibits cytokine production³

- INTERCEPT treatment of units provide protection from TA-GvHD, as well as transfusion-transmitted infections like CMV and bacteria
INTERCEPT PI treatment offers increased safety margins vs. gamma irradiation.

**Gamma irradiation**
Inactivation analyzed using LDA\(^1,2\)

**INTERCEPT**
Inactivation analyzed using LDA at 1.4J/cm\(^2\) \(^3\)

- **Safety Limit** (No TA-GVHD)
  - Radiation dose (cGy)
    - 2,500 cGy

- **Safety Windows**
  - Amotosalen concentration (μM)
    - 150 μM
    - 3 J/cm\(^2\)
Lin L, Corash L, Osselaer J C.

Protection against TA-GvHD due to platelet transfusion using pathogen inactivation with the Intercept blood system™ – Gamma irradiation is not the only answer.

<table>
<thead>
<tr>
<th>Study</th>
<th># of transfusion</th>
<th>Non-gamma irradiated</th>
<th># of patients</th>
<th>Hem-Onc patients</th>
<th>HSCT patients</th>
<th>Incidence of TA-GvHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase III Trials</td>
<td>575</td>
<td>100%</td>
<td>87</td>
<td>82</td>
<td>28</td>
<td>0</td>
</tr>
<tr>
<td>HV1</td>
<td>5,106</td>
<td>97.3%</td>
<td>651</td>
<td>378</td>
<td>47</td>
<td>0</td>
</tr>
<tr>
<td>HV2</td>
<td>7,437</td>
<td>98.9%</td>
<td>1400</td>
<td>748</td>
<td>121</td>
<td>0</td>
</tr>
<tr>
<td>Mont Godinne</td>
<td>3,645</td>
<td>100%</td>
<td>186</td>
<td>186</td>
<td>186</td>
<td>0</td>
</tr>
<tr>
<td>Pediatric</td>
<td>500</td>
<td>100%</td>
<td>83</td>
<td>48</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Basel</td>
<td>551</td>
<td>100%</td>
<td>46</td>
<td>38</td>
<td>15</td>
<td>0</td>
</tr>
</tbody>
</table>
3 groups studied using hemovigilance program:

- Apheresis platelets and buffy coat platelets plus irradiation (2050 patients)
- Same platelets using additive solution plus irradiation (1678 patients)
- Same platelets using additive solution and PI but no irradiation (2069 patients)
Cazenave et al.

Results:
1. Platelet and RBC use per patient not increased after PI implemented.
2. Incidence of acute transfusion reactions was significantly reduced ($p < .001$) after PI implemented.
3. No cases of TA-G-v-HD.
Platelets and plasma indicators for UVA

Vox Sang 2010;99:402
Blood component irradiation alternatives

- Cobalt-60 Source (or linear accelerator unit) in Radiation Therapy Dept.
- Cesium-137 Source in Blood Bank/Center
- X-ray source in Blood Bank/Center
Irradiation of Blood Components

**Dose:** 2500 cGy

**Storage:**
- RBCs lose viability with increasing storage time following irradiation
- Irradiate immediately prior to issue
- Irradiation preferably performed in hospital Blood Banks rather than in Regional Blood Centers
How widely is Blood Irradiation Practiced? Is there a role for Universal Irradiation?

- Approximately 10-15% of red cell units are irradiated in U.S. (2009 NBCUS)
- Irradiation increases the average cost/unit by about $65
- Comprehensive cancer centers and pediatric cancer centers (20-25
Advantages

- Homogeneous dose distribution

Disadvantages

- Blood units must leave blood bank for uncertain length of time, uncertain temp control; difficult coordination, delays
Blood component irradiation:
Cobalt-60 source in radiation therapy

Need to purchase gamma or x-ray irradiation equipment

Inconvenient

Dose uncertainty

Expensive to perform
Blood component irradiation: Cesium-137 source in blood bank/center

One-time capital expenditure

Convenient to use

Dose certain

Long half-life of Cesium-137

Minimal maintenance
### Gamma Irradiators – Gamma Emitters
(Sodium-137, cobalt-60 sources)

*% of blood irradiated in US: CsCl source*

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Device</th>
<th>Radiation source</th>
<th>Strength (Ci)</th>
<th>Chamber size (L)</th>
<th>Central dose rate (cGy/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBL-437C</td>
<td>Gammacell 1000</td>
<td>Cs-137</td>
<td>5100</td>
<td>3.8</td>
<td>1200</td>
</tr>
<tr>
<td></td>
<td>Gammacell 3000</td>
<td>Cs-137</td>
<td>2500</td>
<td>1.0</td>
<td>1800</td>
</tr>
<tr>
<td></td>
<td>Model 143-45</td>
<td>Cs-137</td>
<td>2200</td>
<td>1.4</td>
<td>1250</td>
</tr>
<tr>
<td>Other</td>
<td>Model 143-45A</td>
<td>Cs-137</td>
<td>4000</td>
<td>3.7</td>
<td>1080</td>
</tr>
<tr>
<td></td>
<td>Model 143-68</td>
<td>Co-60</td>
<td>2000</td>
<td>3.2</td>
<td>3000</td>
</tr>
<tr>
<td></td>
<td>Model 109C</td>
<td>Co-60</td>
<td>1800</td>
<td>1.0</td>
<td>940</td>
</tr>
</tbody>
</table>

*Cs-137 source t = 30.2 years, Cobalt-60 source t = 5 years*
Protection of CsCl Sources from Misuse

Background security checks on all staff with unescorted access to irradiator

Constant surveillance by security cameras to immediately detect & respond to unauthorized access

Retrofit device with security enhancements (DOE); Permanent welded closure of rear of irradiator; access to isotopes extremely
Surveillance cameras

Example of Transfusion Line Security Features
Blood component irradiation: X-ray unit in blood bank/center

One-time capital expenditure

Convenient to use

Dose certain

Not radioactive

Moderate maintenance
X-ray Irradiator
(Raycell, Best Theratronics)

- X-ray source
- No NRC license
- 1,566 lbs
- 5 minutes/ 25 Gy cycle
- 1.5 L (2 bags) canister
New!

X-ray Irradiator
(RS 3400 Revolution, Rad Source Technologies)

- X-ray source
- No NRC license
- 1,475 lbs
- 6 minutes/ 25 Gy cycle
- 1-5 500 ml bags cycle
DOSE DISTRIBUTION IN SIMULATED COMPONENTS

Linear Accelerator
Unidirectional, Single Layer

IBL 437C
Lucite Spacer

Gammacell 3000
Lucite Spacer
Estimated cost to switch from a CsCl irradiator to an X-ray irradiator:

- Price of X-ray instrument: $200,000
- Annual maint. Contract: $22,000
- Decommissioning a CsCl irradiator (takes 3-12 mo): $40,000
Use specific indicators for gamma and X-ray irradiation

ISBT 128 Bar Coded Lot Numbers
Gamma Indicators

ISBT 128 Bar Coded Lot Numbers
Gamma Indicators
T-A G-v-H D - summary

• Begins 2-50 days after transfusion
  Fever
  Rash
  Diarrhea
  Liver disease

• Death within 3 weeks (infection 2\(^o\) BM failure)

Prevention can save lives!
References

