Transfusion-associated Graft vs Host Disease (TA-GvHD) and indications for blood product irradiation

Swisstransfusion 2017

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Case 1

- 42-year-old woman, suffering from systemic lupus erythematosus (SLE) since 1991

- Because of refractory lupus nephritis, she received in 1998 three monthly cycles of fludarabine (30 mg/m²/day on Days 1-3) and cyclophosphamide (500 mg/m² on Day 1).

- Three weeks after the last dose of fludarabine, she received, because of severe grade 4 myelotoxicity, 2 units of apheresis platelets (Day 20 and 27), then 2 units of packed RBCs (Day 88) and 6 units of pooled random platelets (Day 90), none of which were irradiated!

TABLE 2. Clinical course after fludarabine administration

<table>
<thead>
<tr>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Cycle 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1</td>
<td>D7</td>
<td>D1</td>
</tr>
<tr>
<td>WBC/µL</td>
<td>8010</td>
<td>3300</td>
</tr>
<tr>
<td>Neut/µL</td>
<td>5520</td>
<td>2700</td>
</tr>
<tr>
<td>Lymphocytes/µL</td>
<td>1520</td>
<td>363</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>10.9</td>
<td>10.2</td>
</tr>
<tr>
<td>Platelets (10³/µL)</td>
<td>378</td>
<td>290</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Fludarabine (mg/m²)</td>
<td>30 x 3</td>
<td>30 x 3</td>
</tr>
<tr>
<td>CY (g/m²) Symptoms</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Δ = platelethapheresis concentrate; ↑ = RBC unit; Δ = random-donor platelet unit; neut = neutrophil; CY = cyclophosphamide.
Case 1

- 10 days after the last transfusion:
  - High fever
  - Diffuse skin rash
  - ↑transaminases and bilirubine
  - Severe pancytopenia
Case 1

- Bone marrow examination shows severe aplasia
- Skin biopsy is compatible with GvHD !!!!
Case 1

- She received anti-thymocyte globulins, cyclosporine and steroids

- An emergency HLA-identical allogeneic PBSC transplantation from her brother was planned, and she received preparatory conditioning

BUT...

- She died of disseminated candidiasis with sepsis and multiorganic failure, before receiving stem cell infusion...
Case 1

Allele-level HLA typing on circulating lymphocytes revealed extra HLA alleles not present in her pretreatment sample, but identical to the HLA haplotypes of an unrelated platelet donor.

<table>
<thead>
<tr>
<th>Day**</th>
<th>Component† or sample</th>
<th>LR‡</th>
<th>HLA-A</th>
<th>HLA-B</th>
<th>HLA DRβ1</th>
<th>DQβ1</th>
<th>DRβ</th>
</tr>
</thead>
<tbody>
<tr>
<td>−60</td>
<td>Patient before fludarabine</td>
<td>–</td>
<td>*24</td>
<td>*5001</td>
<td>*78</td>
<td>*0701</td>
<td>*1301</td>
</tr>
<tr>
<td>+120</td>
<td>Patient during GVHD</td>
<td>–</td>
<td>*24,</td>
<td>*33</td>
<td>*5001,</td>
<td>*78,</td>
<td>*0701</td>
</tr>
<tr>
<td>+20</td>
<td>PC</td>
<td>No</td>
<td>02</td>
<td>02</td>
<td>51</td>
<td>60</td>
<td>–</td>
</tr>
<tr>
<td>+27</td>
<td>PC</td>
<td>No</td>
<td>02</td>
<td>32</td>
<td>44</td>
<td>60</td>
<td>–</td>
</tr>
<tr>
<td>+88</td>
<td>PRBC</td>
<td>Yes</td>
<td>*02</td>
<td>*2301</td>
<td>*15</td>
<td>*4501</td>
<td>*04</td>
</tr>
<tr>
<td>+88</td>
<td>PRBC</td>
<td>Yes</td>
<td>*02</td>
<td>*02</td>
<td>*08</td>
<td>*15</td>
<td>*03</td>
</tr>
<tr>
<td>+90</td>
<td>PLT</td>
<td>No</td>
<td>02</td>
<td>02</td>
<td>13</td>
<td>44</td>
<td>*04</td>
</tr>
<tr>
<td>+90</td>
<td>PLT</td>
<td>No</td>
<td>*01</td>
<td>*2301</td>
<td>*08</td>
<td>*14</td>
<td>*01</td>
</tr>
<tr>
<td>+90</td>
<td>PLT</td>
<td>No</td>
<td>*01</td>
<td>*24</td>
<td>*55</td>
<td>*57</td>
<td>*07</td>
</tr>
<tr>
<td>+90</td>
<td>PLT</td>
<td>No</td>
<td>*01</td>
<td>*26</td>
<td>*18</td>
<td>*55</td>
<td>*11</td>
</tr>
<tr>
<td>+90</td>
<td>PLT</td>
<td>No</td>
<td>*02</td>
<td>*3101</td>
<td>*15</td>
<td>*40</td>
<td>*04</td>
</tr>
<tr>
<td>+90</td>
<td>PLT</td>
<td>No</td>
<td>*02</td>
<td>*24</td>
<td>*27</td>
<td>*40</td>
<td>*04</td>
</tr>
</tbody>
</table>

** Day = day relative to third cycle of fludarabine.
† PC = single-donor platelepheresis concentrate; PLT = random-donor platelet unit.
‡ LR = leukoreduced by filtration.
Case 2

- A 63-year-old white man, retired factory worker, with a **90-pack year tobacco history**, was admitted to the local hospital because of **chest pain** and was found to have **coronary artery disease**

- **Medical history:**
  - S/p curative local radiation therapy for minimally invasive squamous cell carcinoma of the larynx, completed 13 months before admission.
  - Chronic obstructive pulmonary disease (**COPD**)
  - **Peptic ulcer disease**

- On admission to the local hospital, he received 2 doses of **methylprednisolone** (80 mg) for a suspected exacerbation of COPD
  - **Laboratory:** **Hb 85 g/l**, WBC 8.9 G/l with mild lymphopenia (**0.63 G/l**)
  - Bone marrow biopsy (1 day after admission): normocellular marrow.
Case 2

- At the local hospital, he received **4 random units of RBCs**.

- He was then transferred to The Ohio State University Medical Center, Columbus, and underwent **coronary artery bypass graft surgery**, during which he received another **3 units of random packed RBCs**.

- His immediate postoperative course was uncomplicated, and he was discharged 4 days after the operation.

- He sought care at the local hospital **14 days after the initial transfusion** because of:
  - fever (38.9°C)
  - Nausea and vomiting
  - Abdominal pain.
  - **Physical examination**: scleral **icterus**, *asterixis*, and a diffuse, erythematous, **petechial rash** on his trunk and extremities.
## Case 2

### Laboratory findings:

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>80 g/l</td>
<td>Haptoglobin</td>
<td>N</td>
</tr>
<tr>
<td>Creatinine</td>
<td>327 μmol</td>
<td>Urinalysis</td>
<td>N</td>
</tr>
<tr>
<td>ASAT</td>
<td>1231 U/l</td>
<td>Amylase</td>
<td>N</td>
</tr>
<tr>
<td>ALAT</td>
<td>3240 U/l</td>
<td>Lipase</td>
<td>N</td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td>200 U/l</td>
<td>HAV, HBV, HCV, ParvoB19</td>
<td>Neg.</td>
</tr>
<tr>
<td>γ-GT</td>
<td>386 U/l</td>
<td>ANA, RF, anti-mitochondrial Ab</td>
<td>Neg.</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>108 μmol/l</td>
<td>RPR and HIV-1</td>
<td>Neg.</td>
</tr>
<tr>
<td>Direct bilirubin</td>
<td>99 μmol/l</td>
<td>Cerebrospinal fluid</td>
<td>N</td>
</tr>
<tr>
<td>LDH</td>
<td>4360 U/l</td>
<td>Bacterial, mycobacterial, fungal, and viral cultures</td>
<td>Neg.</td>
</tr>
</tbody>
</table>

**Chest radiograph:** left pleural effusion
Case 2

Despite therapy with broad-spectrum antibiotics and vasopressors for hemodynamic support, the patient developed:

- Diarrhea
- Persistant fever
- Worsening encephalopathic symptoms
- Worsening coagulopathy
- Worsening renal function, requiring dialysis.

- **Severe pancytopenia:**
  - WBC count = 0.2 G/l, Tc = 3 G/l and severe anemia requiring multiple transfusions
  - DIC and HIT workup: neg.

Despite aggressive medical management, including mechanical ventilation, the patient’s condition continued to deteriorate and he eventually died from severe digestive hemorrhage.
Case 2: autopsy results

Image 1: Skin biopsy specimen showing mild vacuolar dermatitis with a lymphocytic infiltrate and abundant necrotic keratinocytes (arrow) (H&E, ×400).

Image 2: Portal triad with atypical bile duct epithelium (arrow) and focal lymphocyte invasion (H&E, ×400).

Image 3: Intestinal crypts with apoptosis, marked reactive epithelial changes, and apoptotic debris within lumens (H&E, ×400).

⇒ GvHD !!!
Case 2

HLA typing was performed on the patient and the first 4 RBC donors.

<table>
<thead>
<tr>
<th>Patient and RBC Donor HLA Typing Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA Typing</td>
</tr>
<tr>
<td>Class I</td>
</tr>
<tr>
<td>Patient: A1, A-, B8, B-</td>
</tr>
<tr>
<td>Donor 1: A1, A-, B8, B-</td>
</tr>
<tr>
<td>2: A1, A2, B49, B51, Bw 4</td>
</tr>
<tr>
<td>3: A11, A24, B35, B-, Bw 6</td>
</tr>
<tr>
<td>4: A23, A32, B7, B27, Bw 4, 6</td>
</tr>
<tr>
<td>Class II</td>
</tr>
<tr>
<td>DRB1 <em>0301/4, DRB3</em>; DQB1 *0201/2</td>
</tr>
<tr>
<td>DRB1 *0301/4, DQB1 *0602, *0201/2</td>
</tr>
<tr>
<td>DRB1 <em>0301/4, DRB3</em>; DQB1 *0201/2</td>
</tr>
<tr>
<td>DRB1 <em>0301, DRB4</em>; DQB1 *0602, *0201/2</td>
</tr>
<tr>
<td>DRB1 <em>0301, DRB4</em>; DQB1 *0201/2</td>
</tr>
<tr>
<td>DRB1 <em>0301, DRB4</em>; DQB1 *0602, *0201/2</td>
</tr>
</tbody>
</table>

RBC donor N° 1 was found to have an extended homozygous HLA type for which the patient was heterozygous at the class II region.

Even in the class II region, the donor and recipient shared DQB1 *0201/2.

The implicated donor was male, and the blood was 3 days old at transfusion.
TA-GvHD

Definition:

– Rare but disastrous complication (mortality near 100% !!) of labile blood product (LBP) transfusion containing viable lymphocytes (e.g. erythrocyte concentrates, platelet concentrates, granulocyte concentrates, hematopoïetic stem cells)

– Occurs when immunocompetents lymphocytes are transfused to receiver unable to eliminate them because of:
  • Either immunosuppression (case 1)
  • Or unilateral HLA compatibility (case 2)

– «Engraftment» of transfused lymphocytes leads to host rejection because of immunologic differences.
The receiver will tolerate the donor, as he possesses the same HLA antigens! => Engraftment risk !!!

The donor will attack the receiver because he doesn’t recognize 50% of HLA antigens! ⇒ TA-GvHD risk !!!
⇒ CAVE related donors and populations with important HLA genetic proximity!
## GvHD post-HSCT vs TA-GvHD

<table>
<thead>
<tr>
<th></th>
<th>GvHD post-hematopoïetic stem cell transplantation</th>
<th>TA-GvHD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bone marrow involvement</strong></td>
<td>No</td>
<td>Yes (severe pancytopenia)</td>
</tr>
<tr>
<td><strong>Severity</strong></td>
<td>Variable (+/- =&gt; ++++)</td>
<td>++++ (because of bone marrow aplasia)</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>Depends on GvHD stage (average: 5-10%)</td>
<td>87-100%</td>
</tr>
<tr>
<td><strong>HLA donor / receiver disparity</strong></td>
<td>Mostly low (8 or 9/10; occasionnally 5/10)</td>
<td>Enormous (possibly 0/10 !)</td>
</tr>
<tr>
<td><strong>Intervall of onset</strong></td>
<td>10 to 35 days (aGvHD)</td>
<td>2 to 30 days</td>
</tr>
<tr>
<td><strong>Incidence</strong></td>
<td>30-70% (average: 50%)</td>
<td>0.1-1% of transfusions in susceptible pts</td>
</tr>
</tbody>
</table>
TA-GvHD: Blood products at risk

Any non-frozen blood component containing viable lymphocytes can potentially cause TA-GvHD, even fresh plasma!

<table>
<thead>
<tr>
<th>Blood product</th>
<th>TA-GvHD risk</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thawed frozen RBCs</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Thawed FFP</td>
<td>No</td>
<td>although shown to contain some viable lymphocytes post-thaw</td>
</tr>
<tr>
<td>Granulocytes</td>
<td>Yes (in immunocompromised pts)</td>
<td>Contain many viable lymphocytes</td>
</tr>
</tbody>
</table>

- Minimal number of lymphocytes at risk for TA-GvHD: $\geq 8 \times 10^4$ [1]

- Fresh blood (< 3 days): has been shown to have caused TA-GvHD more commonly than blood that has been stored for longer time (> 7 days), presumably due to decreased viability of lymphocytes on refrigerator storage. [2]

- HLA compatibility: ↑ risk of TA-GvHD (any blood component from relatives or populations with less HLA diversity, such as Japanese).

TA-GvHD: Patients at risk

**Primary T-cell immunodeficiency**
- Congenital T-cell immunodeficiency defects (SCID, DiGeorge syndrome,...)
- Intrauterine transfusions
- Neonatal exchange transfusions

**Acquired T-cell immunodeficiency**
- Allogeneic/autologous hematopoietic stem cell transplant patients
- Patients with Hodgkin’s disease
- Patients treated with T cell immunosuppressive drugs:
  - **Purine analogues** (fludarabine, cladribine, clofarabine, nelarabine,...)
  - ATG (especially rabbit)
  - Alemtuzumab (anti-CD52)
  - Bendamustine?

**N.B:** curiously, no TA-GvHD observed in AIDS or after solid organ transplantations!
TA-GvHD: Patients at risk

Unilateral HLA compatibility

- Likelihood of receiving HLA-compatible (homozygous HLA haplotype to a heterozygous individual sharing one of the same haplotypes) blood during an unrelated transfusion:
  - 1/874 in Japan
  - ~1/7800 in caucasian populations
- Risk of TA-GvHD in immunocompetent patients higher in Japanese (esp. after cardiac surgery and in oncological patients)

- Blood component from relatives
- HLA-compatible blood components

Universal irradiation of LBP:
- Hospitals:
  - MD Anderson, Houston
  - Children’s Hospital, Philadelphia
- Country: Japan
TA-GvHD: Treatment

- Transfusion-associated GvHD has a nearly 100% mortality rate.

- Diagnosis is often missed or delayed, but even with prompt diagnosis, the prognosis is poor.

- Immunosuppression, via medications used to treat BMT-related GvHD, has not been effective in the treatment of TA-GvHD

- Only a few survivors of TA-GvHD have been documented, one after autologous hematopoietic stem cell transplantation\(^1\)

\[=>\] As treatment is almost always unsuccessful, the main thrust for decreasing the risk of TA-GvHD is prevention!

\(^1\) Hutchinson K et al. Transfusion 2002, 1567-1572
TA-GvHD: Prevention by irradiation

Irradiation of cellular blood components has been the mainstay in prevention of TA-GvHD

**Recommended dose:** 25 – 50 Gy

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**Swiss guidelines:**

- **Erythrocyte concentrates:**
  - Can be irradiated within 28 days of collection, but must be transfused within 14 days after irradiation (max. within 28 days after collection)
  - In situations at risk for hyperkaliemia (intrauterine transfusion, neonatal exchange, some infants until 1 year-old)
    - fresh blood (< 5 days) must be used
    - EC must be transfused within 24h after irradiation (48h if infant 0-1 year-old)

- **Platelet concentrates:**
  - All platelet concentrates in CH are PI!
TA-GvHD: Prevention by universal leucodepletion (UL)

- **↓ Incidence of TA-GvHD:**
  - 13 cases of TA-GvHD were reported in the UK between 1996 and 2001, 3 of which were cardiac surgery patients (1 of which received fresh blood).
  - No cases of TA-GvHD in immunocompetent patients have been reported to SHOT since 2001.

- Between 1996 and 2008: 405 near misses (among them, many pts treated with fludarabine)

Has been implemented in many blood center and countries (including CH) because of:
- ↓ leucocyte-associated transfusion-transmitted infectious disease (virus, prions ?)
- ↓ alloimmunization
- ↓ risk of NHTR
- (↓ transfusion-associated immunomodulation)

⇒ Arguments for efficacy of UL!
TA-GvHD: Prevention by pathogen inactivation (PI)

- Implemented in many blood centers and some countries (including CH)

- Replication blockade of nucleic acids, contained in micro-organisms and lymphocytes

- There are several different PI systems:
  - Amotosalen + UV-A illumination (Intercept)
  - Riboflavin + UV-A and UV-B illumination (Mirasol)
  - UV-C (Theraflex)
  - Methylene blue based device

⇒ Inactivated products have NOT to be irradiated

- Until now, no case of TA-GvHD after transfusion of PI products has been reported
TA-GvHD: take home messages

- **Very rare** complication of blood transfusion but **almost always fatal**!

- Think about it when a transfused patient presents (already within **48 hours**) fever, rash, diarrhea, hepatic dysfunction and **pancytopenia**!

- May also occur in **immunocompetent patients**!

- **TA-GvHD treatment outcome is poor**.

- **Prevention** remains the key to reduce the incidence of TA-GvHD.

- Provision of **irradiated cellular blood components** for susceptible recipients has been the mainstay for prevention of the disease.

- In the future, **pathogen inactivation**, with or without universal leucoreduction, may eliminate the need to identify patients at risk.
Thank you for your attention

- Dwyre DM, Holland PV. Vox Sanguinis 2008, 85-93