Management of Hemolytic Anemia Following Allogeneic Stem Cell Transplantation

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Swisstransfusion
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Hemolytic Anemia in the context of HCT

Drug-induced hemolytic anemia (DIHA)

D/R ABO-incompatibility:
- TA-TMA
- D/R ABO-incompatibility:
- Transfusion support

Diseases
- Acute hemolysis
- Passenger lymphocyte syndrome
- Pure red cell aplasia

Conditioning
- Transfusion support

Others: relapse, Infections, PTLD, ...

Donor issues
Hemolytic Anemia in the context of HCT

Drug-induced hemolytic anemia (DIHA)

D/R ABO-incompatibility:
- Acute hemolysis
- Passenger lymphocyte syndrome
- Pure red cell aplasia
- TA-TMA
- AIHA

Transfusion support

Others: relapse, Infections, PTLD, ...

Donor issues

d0

HSCT
Diagnostic Workup

- Knowledge of patient’s and transfusion history, transplant procedure
- Blood count, reticulocytes, blood smear
- Blood chemistry (LDH, bilirubin, haptoglobin)
- Immunohematological investigations:
  - Direct antiglobulin test (DAT)
  - Elution
  - Adsorption techniques
  - Isoagglutinin titering
General Considerations for Management

• Close collaboration between clinicians, stem cell processing facility and transfusion specialists

• Supportive care:
  - **Transfusions**: according to guidelines/SOP
    - Leukocyte-reduced RBC
    - γ-irradiated (25-30 Gy) RBC

• Modification of immunosuppression has to be balanced against an increased risk of GVHD and/or relapse

Kopolovic I et al. Blood 2015; Treleaven J et al. BJH 2010
D/R ABO-Incompatibility

Drug-induced hemolytic anemia (DIHA)

D/R ABO-incompatibility:
- Acute hemolysis
- Passenger lymphocyte syndrome
- Pure red cell aplasia

Transfusion support

D/R ABO-Incompatibility:
- TA-TMA
- AIHA

Others: relapse, Infections, PTLD, ...

Donor issues

d0 HSCT
D/R ABO-Incompatibility

• Human leukocyte antigens (HLA) genes are located on chromosome 6 (6p21)

• Genes encoding transferases for ABO blood groups are located on chromosome 9 (9q34)

• Independent inheritance of HLA genes and ABO blood groups

• ABO-incompatible HCT occurs in 30-50% of patients

Booth GS et al. BBMT 2013
D/R ABO-Incompatibility

- ABO-incompatibility is **not** a barrier to HCT but increases the **complexity** of the procedure

- (Probably) **no** effect on major transplant outcomes (engraftment, graft failure, GVHD, relapse, TRM, OS)

- **Heterogeneous** studies: registry studies, retrospective/single center studies

Rowley SD et al. BMT 2011; Seebach JD et al. BBMT 2005; Worel N. Transfus Med Hemother 2016
D/R ABO-Incompatibility

- **Major** ABO-Incompatibility (20-25%):
- **Minor** ABO-Incompatibility (20-25%):
- **Bidirectional** ABO-Incompatibility (3-5%)

Gajewski JL et al. Blood 2007; Rowley SD et al. BMT 2011; Booth GS et al. BBMT 2013
Daniel-Johnson J et al. Transfusion 2011
Major D/R ABO-Incompatibility

- **Acute hemolysis** of donor RBC
  - Graft source: HPC(M) > HPC(A)/HPC(C)
  - Prevention:
    - RBC depletion of the graft (apheresis, sedimentation)
    - Reduction of isoagglutinins in the recipient
  - Hydration, monitoring for acute hemolytic reactions

Major D/R ABO-Incompatibility

- **Delayed RBC engraftment**, increased transfusion requirement
- **Pure red cell aplasia** (PRCA):
  - Reticulocytopenia >60 days, absent erythroid precursors in the marrow in a recipient who has otherwise engrafted
  - Ongoing isoagglutinin production by persistent recipient plasma cells
  - Hemolysis of donor RBC and inhibition of donor erythropoiesis (destruction of erythroid progenitors)

**Major D/R ABO-Incompatibility**

- **Pure red cell aplasia** (PRCA)
  - Incidence: 5-(50)%, risk factors: age, donor blood group A, conditioning (RIC > MAC)
  - Management:
    - Transfusions (donor and recipient compatible RBCs)
    - Immunomodulation:
      - Reduction of immunosuppression (graft versus plasma cell effect), donor lymphocyte infusions
      - Reduction of isoagglutinins: plasma exchange or rituximab*

Minor D/R ABO-Incompatibility

- **Acute hemolysis**: donor plasma with high isoagglutinin titers or recipients with small blood volume
  - Plasma reduction
  - Hydration, monitoring for acute hemolytic reactions

Fung MK et al. AABB Technical Manual 2014
Minor D/R ABO-Incompatibility

- **Passenger lymphocyte syndrome**: viable „passenger“ lymphocytes in the graft secrete anti-host isoagglutinins
  - Delayed transfusion reaction 5-15 days after HCT
  - Incidence: 10-15% of minor ABO-incompatible HCT
  - Risk factors: HPC(A) > HPC (M), D/R: O/A, CYA alone as GVHD prophylaxis, RIC > MAC
  - DAT +, donor-derived isoagglutinins, positive eluate against recipient‘s blood group

Bolan CD et al. BJH 2001
Minor D/R ABO-Incompatibility

• Passenger lymphocyte syndrome
  - Prevention/Management:
    - Beginning pre HCT to dilute recipient‘s RBC < 30%:
      - Transfusions (blood group O)
      - RBC exchange
    - Monitoring for delayed hemolytic reactions
    - Hydration, preservation of kidney function, transfusions

Donor  ➔  Recipient

Non-ABO D/R RBC-Incompatibility

- Less frequent, as donors and recipients lack “naturally” formed antibodies against non-ABO RBC antigens
- Anti-D alloimmunization after D-mismatched HCT and development of other new non-ABO RBC alloantibodies is rare
- Involved systems: Rhesus/Kell/Kidd/Duffy/MNSs/Lewis
- Delayed hemolytic anemia or passenger lymphocyte syndrome (2-9%)
- Antibodies against third party antigens (transfused RBC)

Franchini M et al. BMT 1998; de la Rubia J et al. Transfusion 2001; Young PP et al. BMT 2001; Cid J et al. Transfusion 2006
Platelet/Plasma Transfusion and...

- **Platelet** transfusions: platelet components contain plasma and thus isoagglutinins
- **Platelets** express ABO blood groups
- **Plasma**: transfusion of both donor- and recipient-compatible plasma

- **IVIG** may cause hemolysis

- Consider always potential **transfusion errors**
## Transfusions

<table>
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<th>ABO incompatibility</th>
<th>D</th>
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<th>RBC transfusion</th>
<th>PLT transfusion</th>
<th>Plasma transfusion</th>
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Conditioning

Drug-induced hemolytic anemia (DIHA)

D/R ABO-incompatibility:

TA-TMA

Diseases

Acute hemolysis

Passenger lymphocyte syndrome

Pure red cell aplasia

AIHA

Conditioning

Transfusion support

d0

HSCT

Donor issues

Others: relapse, Infections, PTLD, ...
Transplantation-Associated Thrombotic Microangiopathy

- TA-TMA is a severe complication after HCT associated with long-term morbidity, chronic organ injury and high mortality
- Incidence: 10-35%
- The pathogenesis of this multi-system disorder is unknown
- Various triggers (including chemotherapy, irradiation, immunosuppressive agents, GVHD, infections) cause endothelial injury leading to organ damage
- Increasing evidence of dysregulation/activation of the complement system (≈aHUS)
- Role of complement gene variants (genes & environment)

TA-TMA Diagnosis: Histology

Siami K et al. Transplantation 2008
**TA-TMA Diagnosis: non-invasive**

- **No** universally accepted criteria, high index suspicion
- **Laboratory and clinical markers:**

<table>
<thead>
<tr>
<th>BMT CTN</th>
<th>IWG EBMT/ELN</th>
<th>Cincinnati/Philadelphia</th>
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<tbody>
<tr>
<td>Schistocytes</td>
<td>Schistocytes (&gt;4%)</td>
<td>Schistocytes</td>
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<td>LDH ↑</td>
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<td>LDH ↑</td>
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<td>Renal ± neurologic dysfunction</td>
<td>Thrombocytopenia</td>
<td>Thrombocytopenia</td>
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<tr>
<td>DAT negative</td>
<td>Anemia</td>
<td>Anemia</td>
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<tr>
<td></td>
<td>Haptoglobin ↓</td>
<td>Hypertension</td>
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<td>Proteinuria*</td>
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<td></td>
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<td>sC5b-9 ↑*</td>
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</table>

TA-TMA Diagnosis: non-invasive

Cho et al.  
No DIC  
Thrombocytopenia, Anemia  
Cincinnati/Philadelphia

BMT CTN  
Renal ± neurologic dysfunction  
DAT negative  
Schistocytes, LDH↑  
Hypertension, Proteinuria, sC5b-9↑

EBMT/ELN  
Haptoglobin↓

• **Proteinuria, sC5b-9↑** (and anemia <80g/l) at the time of TMA diagnosis are associated with increased risk of death
## TA-TMA Manifestations

<table>
<thead>
<tr>
<th>Organ</th>
<th>Manifestation</th>
<th>Differential diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidneys</td>
<td>Proteinuria, hypertension, decreased function</td>
<td>Nephrotoxic drugs, infections, steroids, CYA</td>
</tr>
<tr>
<td>Lungs</td>
<td>Pulmonary hypertension, Hypoxia</td>
<td>Infections, BOS/GVHD</td>
</tr>
<tr>
<td>GI</td>
<td>Diarrhea, vomiting, abdominal pain, bleeding, ileus</td>
<td>Infections, GVHD, thrombocytopenic bleeding</td>
</tr>
<tr>
<td>CNS</td>
<td>Confusion, headache, hallucinations, seizures</td>
<td>Drugs, infections, bleeding, PRES, CNS-disease</td>
</tr>
</tbody>
</table>

TA-TMA Treatment

• **Supportive:**
  - withdrawal/reduction/replacement of immunosuppression (CYA/tacrolimus/sirolimus → steroids? Mycophenolate?)
  - Antihypertensive medication (ACE inhibitors; angiotensin receptor blockers)
  - Treatment of infections and/or GVHD
  - Dialysis
  - Transfusions

TA-TMA Treatment

• **Causative:**
  - **Eculizumab*** (complement blockade)
    Indication: patients with proteinuria and sC5b-9 ↑
    Consider dosage regimen
  - Others (case reports)*: rituximab, defibrotide, vincristine, pravastatin, rTM

Plasma infusions and TPE are generally not recommended
(ASFA 2016: 2C/III)

TA-TMA Issues

• Common **definition criteria**

• Promote further prospective, multi-center studies to
  - identify more specific and early disease **markers**
  and
  - evaluate new **therapeutic** agents
Autoimmune Hemolytic Anemia after HCT

Diseases:
- Drug-induced hemolytic anemia (DIHA)
- Acute hemolysis
- Passenger lymphocyte syndrome
- Pure red cell aplasia

D/R ABO-incompatibility:
- TA-TMA

Donor issues:
- D/R ABO-incompatibility: Acute hemolysis
- Pure red cell aplasia

Transfusion support

Others: relapse, Infections, PTLD, ...

d0
HSCT
Autoimmune Hemolytic Anemia

• Autoimmune diseases after HCT ≈ GVHD (?)

• Incidence of AIHA: 1-4%

• Risk factors: unrelated donor, cGVHD, lymphodepletion, non-malignant disease

• Median time of onset of AIHA after HCT: 5-12 months

• Therapy resistant and associated with increased mortality

Drobyski WR et al. BMT 1996; Sanz J et al. BMT 2007; Faraci M et al. BBMT 2014; Wang M et al. BBMT 2015
AIHA Diagnosis

• AIHA diagnosis may be difficult
  
  Autoimmune hemolytic anemia

• (normocytic) Anemia (and reticulocytosis)?

• Hemolysis? Bilirubin ↑, LDH ↑, haptoglobin ↓, hemoglobinemia, hemoglobinuria

• Autoimmune: DAT (usually) + for C3d, IgG/IgM or both

• And: don’t forget the blood smear!

# AIHA Differential Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Warm AIHA</th>
<th>Cold AIHA</th>
<th>Mixed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoantibody (Antigen)</td>
<td>IgG (Rh)</td>
<td>IgM (I/i)</td>
<td>IgG &amp; IgM</td>
</tr>
<tr>
<td>Clinic</td>
<td>Extravascular</td>
<td>Intravascular</td>
<td>Combined</td>
</tr>
<tr>
<td>DAT</td>
<td>IgG +/- C3 (IgG1, IgG3)</td>
<td>C3 alone</td>
<td>IgG + C3</td>
</tr>
</tbody>
</table>

Supportive:

- Transfusions: serologic incompatibility of (all) crossmatched donor erythrocytes → Labor-intensive and time consuming techniques
  - Do not withhold transfusions in critical cases!
  - Physician’s decision (and responsibility), close monitoring
  - Selection of RBC depending on urgency
AIHA Treatment

- **Causative:**
  - Immunosuppression has to be balanced against a possible increased risk of disease relapse
  - No consensus on the optimal therapeutic approach, very low evidence (case reports, case series)

A) **WAIHA:** - First-line: corticosteroids
  - Second-line: rituximab* or splenectomy
  - Others: danazol, cyclophosphamide, azathioprine, mycophenolate mofetil, cyclosporine, sirolimus

AIHA Treatment

B) **CAIHA:**  - Avoidance of cold temperatures, warm transfusions (if needed) and infusions
  - Indications for treatment: symptomatic anemia, transfusion dependence, disabling circulatory symptoms
  - Rituximab* (+/- fludarabine)
  - Plasma exchange (ASFA 2016: 2C/II)
  - Eculizumab*

Summary

Drug-induced hemolytic anemia (DIHA)

D/R ABO-incompatibility:
- Acute hemolysis
- Passenger lymphocyte syndrome
- Pure red cell aplasia
- TA-TMA
- AIHA

Transfusion support

D0
- HSCT

Others: relapse, Infections, PTLD...

Donor issues
Thank you!
TA-TMA Differential Diagnosis

- Thrombotic thrombocytopenic purpura (inherited, acquired)
- Classical hemolytic uremic syndrome (Shiga toxin-producing *Escherichia coli*)
- Atypical hemolytic uremic syndrome (complement mediated)
- Transplantation-associated thrombotic microangiopathy*
- Pregnancy associated (HELLP-syndrome, Pre-eclampsia, Eclampsia)
- Disseminated intravascular coagulation*
- Drug-induced thrombotic microangiopathy (immune mediated, toxic)*
- Infections*
- Malignant hypertension*
- Malignancy
- Autoimmune