Transfusion bei (allogener) Stammzelltransplantation

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Bern
O neg /
Don’t transfuse more units of blood than absolutely necessary.

Each unit of blood carries risks. A restrictive threshold (7.0-8.0 g/dL) should be used for the vast majority of hospitalized, stable patients without evidence of inadequate tissue oxygenation (evidence supports a threshold of 8.0 g/dL in patients with pre-existing cardiovascular disease). Transfusion decisions should be influenced by symptoms and hemoglobin concentration. Single unit red cell transfusions should be the standard for non-bleeding, hospitalized patients. Additional units should only be prescribed after re-assessment of the patient and their hemoglobin value.

Don’t transfuse red blood cells for iron deficiency without hemodynamic instability.

Blood transfusion has become a routine medical response despite cheaper and safer alternatives in some settings. Pre-operative patients with iron deficiency and patients with chronic iron deficiency without hemodynamic instability (even with low hemoglobin levels) should be given oral and/or intravenous iron.

Don’t routinely use blood products to reverse warfarin.

Patients requiring reversal of warfarin can often be reversed with vitamin K alone. Prothrombin complex concentrates or plasma should only be used for patients with serious bleeding or requiring emergency surgery.

Don’t perform serial blood counts on clinically stable patients.

Transfusion of red blood cells or platelets should be based on the first laboratory value of the day unless the patient is bleeding or otherwise unstable. Multiple blood draws to recheck whether a patient’s parameter has fallen below the transfusion threshold (or unnecessary blood draws for other laboratory tests) can lead to excessive phlebotomy and unnecessary transfusions.

Don’t transfuse O negative blood except to O negative patients and in emergencies for women of child bearing potential with unknown blood group.

O negative blood units are in chronic short supply due in part to overutilization for patients who are not O negative. O negative red blood cells should be restricted to: (1) O negative patients; or (2) women of childbearing potential with unknown blood group who require emergency transfusion before blood group testing can be performed.
Agenda

• General issues in hematological patients
• Stem cells, transplant patients and basics of hematopoietic stem cell transplantation (HSCT)
• Blood group incompatibility
• Hemolytic anemia in patients after HSCT
• RBC transfusions
• Pitfalls in the lab
• (Platelet transfusions)
Different patient populations are different

**Surgical/critical care patients:**
- Acute anemia
- Intravascular volume depleted
- Normal erythropoietic reserve
- Self-limiting illness
- Responsive to nutritional therapy and short term transfusion
- Inpatient

**Hematology patients:**
- Chronic anemia
- Intravascular volume expanded
- Minimal to no erythropoietic reserve
- Long-term illness
- Rarely responsive to nutritional therapy and requires long term transfusion support
## RCT comparing RBC transfusion strategies in patients with AL or undergoing HSCT

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
<th>Intervention</th>
<th>Primary outcomes</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Webert et al.</td>
<td>Adults AL or allo HSCT (n=60)</td>
<td>80 vs. 120 g/l</td>
<td>Feasibility Bleeding</td>
<td>- Feasible - No difference in bleeding</td>
</tr>
<tr>
<td>Robitaille et al.</td>
<td>Children allo HSCT (n=6)</td>
<td>70 vs. 90 g/l</td>
<td>Neutrophil recovery</td>
<td>Study terminated</td>
</tr>
<tr>
<td>TRIST (NCT 01237639)</td>
<td>Adults auto or allo HSCT (n=30)</td>
<td>70 vs. 90 g/l</td>
<td>QoL</td>
<td>Recruiting</td>
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<tr>
<td>Chantepie et al. (NCT 02461264)</td>
<td>Adults AL, AA, auto/allo HSCT</td>
<td>1 U vs. 2 U for Hb &lt; 80 g/l</td>
<td>Complication rate</td>
<td>Recruiting</td>
</tr>
<tr>
<td>DeZern A et al. (NCT 0286773)</td>
<td>Adults AL (n=90)</td>
<td>70 vs. 80 g/l</td>
<td>Safety and feasibility</td>
<td>Preliminary results (ASH 2015)</td>
</tr>
</tbody>
</table>
RCT comparing RBC transfusion strategies

Stem cells

Transplant patients

• Malignant and (> ) non-malignant diseases
• (Good) indication for HSCT
• Disease remission
• Comorbidities
• Availability of a suitable donor
Hematopoietic stem cell transplantation

• Autologous vs. allogeneic HSCT
• Allogeneic HSCT:  - donor (MRD; MUD; others)
                   - stem cell source:
Allogeneic hematopoietic stem cell transplantation

Diagnosis

(Diagnosis)

<table>
<thead>
<tr>
<th>(Chemo-)therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease remission?</td>
</tr>
</tbody>
</table>

HSCT

Complications: infections, GVHD, relapse, toxicity

- Aplasia
- Transfusion support

Chemo-/Radiotherapy: anti-tumour and immunosuppression
Indications (Europe)

Passweg JR et al. BMT 2015
Hematopoietic stem cell transplantation in Europe

Passweg JR et al. BMT 2015
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
D/R ABO-Incompatibility

- **Major** ABO-Incompatibility (20-25%): 
  - Donor
  ![Diagram of major ABO-incompatibility](image)

- **Minor** ABO-Incompatibility (20-25%): 
  - Donor
  ![Diagram of minor ABO-incompatibility](image)

- **Bidirectional** ABO-Incompatibility (3-5%)
  - Donor
  ![Diagram of bidirectional ABO-incompatibility](image)

References:
- 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, Transfusions

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
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

Minor D/R ABO-Incompatibility

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
Hemolytic Anemia in the context of HCT

Drug-induced hemolytic anemia (DIHA)

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

Diseases

Conditioning

Donor issues

d0
HSCT

Others: relapse, Infections, PTLD, ...

Transfusions

O neg /
General Considerations for Transfusions

- Close collaboration between clinicians, stem cell processing facility and transfusion specialists
- Supportive care:
  - **Transfusions**: according to guidelines/SOP
    - Leukocyte-reduced RBC (Standard of care in CH):
      - Prevention of alloimmunization
      - Prevention of CMV transmission
      - Prevention of FTR
      - Prevention of immunomodulatory effects (...!?)
    - γ-irradiated (25-30 Gy) RBC

Kopolovic I et al. Blood 2015; Treleaven J et al. BJH 2010
Leukocyte-reduced RBC

Immunologic effects
  Alloimmunization
    Febrile nonhemolytic transfusion reactions
    Refractoriness to platelet transfusion
    Rejection of transplanted organs
  Graft-versus-host disease
  Transfusion-related acute lung injury
Immunomodulation
  Increased bacterial infections
  Increased recurrence of malignancy
Infectious disease
  Cytomegalovirus
  Human T-lymphotrophic virus-I
  Epstein–Barr virus

Transfusion-associated GVHD (TA-GVHD)

- Transfused, blood-derived alloreactive T-lymphocytes attack host tissues
- TA-GVHD presents within 2-30 d following transfusion
- (Almost: 90-100%) letal
- But: HLA similarity between donor and recipient plays an important role
  - Host immune deficits
  - Component characteristics
  - Donor/recipient HLA relationship

**Indications for irradiation of blood components for prevention of TA-GVHD:**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stem cell transplant recipients</td>
<td>✓</td>
</tr>
<tr>
<td>Congenital immunodeficiencies or infants with features suggestive of an undiagnosed immunodeficiency</td>
<td>✓ ✓ ✓</td>
</tr>
<tr>
<td>Intrauterine transfusion</td>
<td>✓ ✓ ✓</td>
</tr>
<tr>
<td>Premature, low birth weight</td>
<td>✓ ✓ ✓</td>
</tr>
<tr>
<td>Term infants (&lt;6 months old)</td>
<td>✓ ✓ ✓</td>
</tr>
<tr>
<td>Acute lymphoplastic leukemia</td>
<td>✓ ✓ ✓</td>
</tr>
<tr>
<td>Other lymphoid malignancies</td>
<td>✓ ✓ ✓</td>
</tr>
<tr>
<td>Acute myeloid leukemia</td>
<td>✓ ✓</td>
</tr>
<tr>
<td>Chronic leukemias</td>
<td>✓</td>
</tr>
<tr>
<td>Stem cell donors during harvest</td>
<td>✓</td>
</tr>
<tr>
<td>Fludarabine, alemtuzumab, and ATG recipients</td>
<td>✓ ✓ ✓</td>
</tr>
<tr>
<td>Children on intensive myeloablative chemotherapy regimens</td>
<td>✓ ✓</td>
</tr>
<tr>
<td>Children with solid tumors or malignant hematologic disease</td>
<td>✓ ✓ ✓</td>
</tr>
<tr>
<td>Children with solid organ transplants</td>
<td>✓</td>
</tr>
</tbody>
</table>

HSC, Hospital for Sick Children, Toronto, Canada; MGH, Massachusetts General Hospital, Boston, MA; SBK, Sunnybrook Health Sciences Centre, Toronto, Canada; UHN, University Health Network, Toronto, Canada.

Kopolovic I et al. Blood 2015
Transfusion-associated GVHD (TA-GVHD)

- Intrauterine Transfusionen und Frühgeburten
- Kinder mit angeborenem kombinierten Immundefekt (SCID)
- Erworbene Immundefizienz:
  - Allogene und autologe HSCT
  - Chemotherapie bei Leukämien
  - Therapie mit Purinanaloga
- Anti T-Zell Behandlung
- EK/TK-Transfusion zwischen 1.-3.gradigen Verwandten
- HLA-kompatible TK
- Granulozytentransfusionen
- Allogene und autologe Stammzellspender
- M. Hodgkin
Transfusion-associated GVHD (TA-GVHD)

- Leukoreduktion alone is inadequate to prevent TA-GVHD

- γ-irradiation (25-30 Gy) is standard of care for the prevention of TA-GVHD, mainly in patients with immune defects

# Transfusions

<table>
<thead>
<tr>
<th>ABO incompatibility</th>
<th>D</th>
<th>R</th>
<th>RBC transfusion</th>
<th>PLT transfusion</th>
<th>Plasma transfusion</th>
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<tbody>
<tr>
<td><strong>Major</strong></td>
<td></td>
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<td></td>
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<tr>
<td>A O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>AB or A</td>
<td>AB or A</td>
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<tr>
<td>B O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>AB or B</td>
<td>AB or A</td>
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<tr>
<td>AB O</td>
<td>O</td>
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<td>O</td>
<td>AB</td>
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<tr>
<td>AB A</td>
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<td>O or B</td>
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<tr>
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<td>O or A</td>
<td>AB or A</td>
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<td>O B</td>
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<td>AB or B</td>
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<td>O AB</td>
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<td>A AB</td>
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<tr>
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<td>B A</td>
<td>O</td>
<td>O</td>
<td></td>
<td>AB</td>
<td>AB</td>
</tr>
</tbody>
</table>

**Pitfalls in the lab**

- **Pre-transplant examinations:**
  - Extended RBC phenotyping (genotyping if previous transfusions)
  - Determination of isoagglutinins
  - Direct antiglobulin test (DAT)
- **Peri/post-transplant:**
  - Direct antiglobulin test (DAT)
  - Elution (also against non O RBC panel!)
  - Adsorption techniques
  - Isoagglutinin titering
Pitfalls in the lab

- Months after transplantation:
  - Switch to donor ABO-blood group
  - Maintenance of secretor status (Lewis)
  - No detection of isoagglutinins after HSCT (B-cell toleranace?)
- Cave: relapse!

Stussi G et al. Transplant Proc 2005
Platelet/Plasma Transfusion and...

- **Platelet** transfusions: platelet components contain plasma and thus isoagglutinins
- **Platelets** express ABO blood groups
- **No** irradiation of platelets after introduction of pathogen-reduced components
- **Plasma**: transfusion of both donor- and recipient-compatible plasma

- **Granulocyte** transfusions (...)

Fast LD. BJH 2012; Estcourt LJ et al. Cochrane Collaboration 2015
### Platelet transfusions

**Platelet transfusions triggers:**

<table>
<thead>
<tr>
<th>Platelet Count</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5x10^9/l</td>
<td>Stable chronic thrombocytopenia (e.g., aplastic anemia)</td>
</tr>
<tr>
<td>&lt;10x10^9/l</td>
<td>Thrombocytopenia under chemotherapy and after stem cell transplantation</td>
</tr>
<tr>
<td>&lt;20x10^9/l</td>
<td>Fever, mucositis, or GvHD, acute promyelocytic leukemia, light bleeding (e.g., petechia, nasal bleeding, microhematuria) before ATG therapy, liver biopsy, transjugular, small operative procedures (e.g., foot, arthroscopy, VAC exchange), bronchoscopy, ZVK placement, lumbar puncture</td>
</tr>
<tr>
<td>&lt;30x10^9/l</td>
<td>Prophylactic and therapeutic anticoagulation, moderate bleeding (e.g., macrohematuria), gastroscopy also with biopsy</td>
</tr>
<tr>
<td>&lt;50x10^9/l</td>
<td>Severe bleeding (e.g., intracerebral, gastrointestinal), spinal anesthesia, liver biopsy, transcutaneous, bronchoscopy with biopsy, large operative procedures and procedures with high bleeding risk, mass transfusion (s.2.1.2.), lifethreatening bleeding due to DIC</td>
</tr>
<tr>
<td>&lt;80x10^9/l</td>
<td>Epidural anesthesia</td>
</tr>
<tr>
<td>&lt;100x10^9/l</td>
<td>Ophthalmological procedures, neurosurgical procedures</td>
</tr>
<tr>
<td>No indication</td>
<td>Bone marrow biopsy (if adequate compression is not achieved)</td>
</tr>
<tr>
<td>Above value</td>
<td>Bleeding due to thrombocytopenia dysfunction, e.g., medication causes</td>
</tr>
</tbody>
</table>

**Indikationen zur Thrombozyten substitution bei normaler plasmatischer Gerinnung und fehlender Einnahme von Thrombozytenaggregationshemmer:**

- Fieber, Mukositis, oder GvHD
- Akute Promyelozyten Leukämie (solange Hyperfibrinolyse)
- Leichte Blutung (z.B. Petechien, Nasenbluten, Mikrohamaturie) vor ATG Therapie
- Leberbiopsie, transjugulär
- Kleinere operative Eingriffe (z.B. Halux, Arthroskopie, VAC-Wechsel)
- Bronchoskopie
- ZVK Anlage
- Lumbalpunktion

**Transfusionsleitfaden USB**
• **Prophylactic or therapeutic platelet** transfusions:
  - Wandt H et al.: therapeutic strategy could become standard of care for clinically stable patients with **autologous HSCT**

  - TOPPS trial: WHO grade 2-4 bleeding was reduced by 7% with prophylactic transfusions (but 61% more PLT transfusions!)
Platelet transfusions

- Platelet transfusion **refractoriness**

  - Immune factors (<20%)
    - HPA (10-20%)
    - HLA-I (80-90%)
    - Auto immune
    - HLA & HPA (5%)

  - Non-immune factors
    - Sepsis/fever, DIC, Splenomegaly, active Bleeding, drugs,...

Pavenski K et al. Tissue Antigens 2012
Thank you!
History

- 1955: Initial report on use of BMT as cancer treatment
- 1960: Successful canine littermate BMT
- 1965: BMT for radiation accident
- 1970: Cure of lymphoma with autologous BMT
- 1975: Allogeneic BMT for aplastic anemia
- 1980: Recognition of human graft-versus-leukemia effect
- 1985: Cure of sickle cell anemia with BMT
- 1990: Successful transplantation from unrelated donor
- 1995: Remission with donor lymphocyte infusion
- 2000: Introduction of reduced-intensity transplants
- 2005: Imatinib mesylate for chronic myelogenous leukemia
- 2010: Publication of negative breast cancer study
Hematopoietic stem cell transplantation in Europe

Passweg JR et al. BMT 2015
### Transfusion-associated GVHD (TA-GVHD)

#### Table A

<table>
<thead>
<tr>
<th></th>
<th>HLA I</th>
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<tbody>
<tr>
<td></td>
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<td>(D=0)</td>
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<tr>
<td>(D≥1)</td>
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<td>264</td>
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#### Table B

<table>
<thead>
<tr>
<th>Recipient immune status</th>
<th>Donor HLA status</th>
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</thead>
<tbody>
<tr>
<td>Irradiation not indicated</td>
<td>(D=0)</td>
<td>(D≥1)</td>
</tr>
<tr>
<td></td>
<td>55</td>
<td>2</td>
</tr>
<tr>
<td>Irradiation indicated</td>
<td>5</td>
<td>7</td>
</tr>
</tbody>
</table>

Kopolovic I et al. Blood 2015