Engraftment

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Engraftment

• The stem cells of the donor have been taken up by the patient’s bone marrow ("have engrafted")
Stem cell transplantation

Conditioning

Infusion of graft

Neutrophils

0.5 x 10⁹/L

days
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Definition of engraftment

- The first of three days with neutrophil count $> 0.5 \times 10^9/L$
Failure of engraftment

- No engraftment: neutrophils never reach $\geq 0.5 \times 10^9/L$ (primary graft failure)

- Lost graft: neutrophils increase to $\geq 0.5 \times 10^9/L$ and subsequently decrease to a lower level until additional treatment to obtain engraftment is given (secondary graft failure)
Engraftment: notes

- Neutrophils can temporarily decrease to lower levels (< 0.5 x 10^9/L) due to several causes such as viral infections, medication or graft versus host disease. This is not a lost graft.

- There can be a loss of an allogeneic graft with normal blood cell counts due to autologous reconstitution. This can be confirmed with chimerism studies.
Haematopoietic reconstitution

- First of three consecutive days with the indicated blood cell levels:
  - Neutrophils > 0.5 x 10⁹/L
  - Leucocytes > 1.0 x 10⁹/L
  - Platelets (without transfusion) > 20 x 10⁹/L
  - Platelets (without transfusion) > 50 x 10⁹/L

Without transfusion: no transfusions for at least seven days before reconstitution is recorded.
Haematopoietic reconstitution

- It is possible that the blood cell levels never go below the given limit. This is possible in transplantations with reduced intensity (non-myeloablative) conditioning.

- It is possible, without loss of graft, that some blood cell counts do not reach the given limit for a very long time (particularly platelets)
Stem cell transplantation

- Conditioning
- Infusion of graft
- Neutrophils
- 0.5 x 10^9/L
Haematopoietic chimaerism

"Chimaera": creature from Greek mythology whose body is made of parts from different animals

In allogeneic transplantation chimerism is normally used to describe the status of donor marrow in the patient.
Chimaerism

- Can be studied from bone marrow or peripheral blood, and from different blood cell populations:
  - total cell population
  - T cells and subpopulations
  - B cells
  - NK cells
  - myeloid cells
  - CD34+ cells
Methods to study chimaerism

- Fluorescent in situ hybridization (FISH)
  - if sex difference between donor and recipient
- Variable number of tandem repeats (VNTR)
- Short tandem repeats (STR)
  (Microsatellites: STR, VNTR)
- Red cell phenotypes
- Restriction fragment length polymorphism (RFLP)
Figure 1. Results of quantifying chimerism by STR-PCR (A; peak constellation for the informative marker D3S1358 is shown as an example) and XY-FISH (B; photomicrograph of the 50% male/50% female peripheral blood smear is shown as an example) in the first set of artificial mixtures (first experiment) with known proportions of male and female cells. EXP. Percentage of male (recipient) cells in the artificial mixtures. OBS. Percentage of male (recipient) cells observed with each method.
Schematic of a Variable Number of Tandem Repeats in 4 alleles.
Chromosomal locations of the 13 VNTR loci in the CODIS panel.
Variations of VNTR (D1S80) allele lengths in 6 individuals.
Fluorescence-based PCR amplification of short tandem repeats (STR) and capillary electrophoresis from whole peripheral blood is the most widely used method.
Chimaeric situations

- Full donor chimerism: > 95% of cells from the donor
- Mixed or partial chimaerism: cells are both from the donor and the recipient
  - recipient cells decreasing
  - recipient cells increasing
  - stable
- Split chimaerism
- Autologous reconstitution: no donor cells, all cells from the recipient
- Aplasia: no cells, empty marrow
Causes of graft failure

- Immunological rejection
  - Recipient’s T-cells
- Viral infections
  - Cytomegalovirus (CMV)
  - Human herpes virus type 6 (HHV6)
  - Parvovirus
- Drug toxicity
- Septicaemia
Risk factors for graft failure

- Major histocompatibility complex (MHC) disparity between recipient and donor
- Unrelated donor
- Sensitization caused by blood transfusions or pregnancy
- Low cell dose in the graft
- T-cell depletion
- Reduced intensity ("nonmyeloablative") conditioning
- Cord blood transplantation
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Haplo/T-cell Dep

MUD

Matched Sibling

Immunosuppression

True nonablative  Reduced toxicity  Ablative

Myelosuppression

F-TBI
2 Gy

MF 140

Bu8/F/ATG
Bu 16/Cy

TT-C

TT, M-ATG

MF 180

Bu16/Cy

TBI/Cy

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Prevention of graft failure

- Choice of donor
- Intensified conditioning
- High cell dose
- ATG
Cellular therapy for imminent graft failure or poor graft function

- Donor lymphocyte infusions
- Boost of donor stem cells
Treatment of graft failure

- Treatment of underlying cause
  - GvHD, infection

- Growth factors

- Retransplantation
  - Same or other donor
  - Preferably different conditioning
  - Intensive immunosuppression
  - High cell dose