Stem cell transplantation

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HSC transplantation

- **Principle:**

- Stem cell transplantation (SCT) involves removal of patient's haemopoietic and immune system by chemotherapy and/or radiotherapy and replacing it with stem cells.

- Transplanted stem cells can be allogeneic (from another individual) or autologous (previously harvested portion of the patient's own HSCs), or syngeneic (from identical twins).

Sources of HSCs

1- Bone Marrow:

- When HSCs are collected from BM the term *bone marrow transplantation* is used.

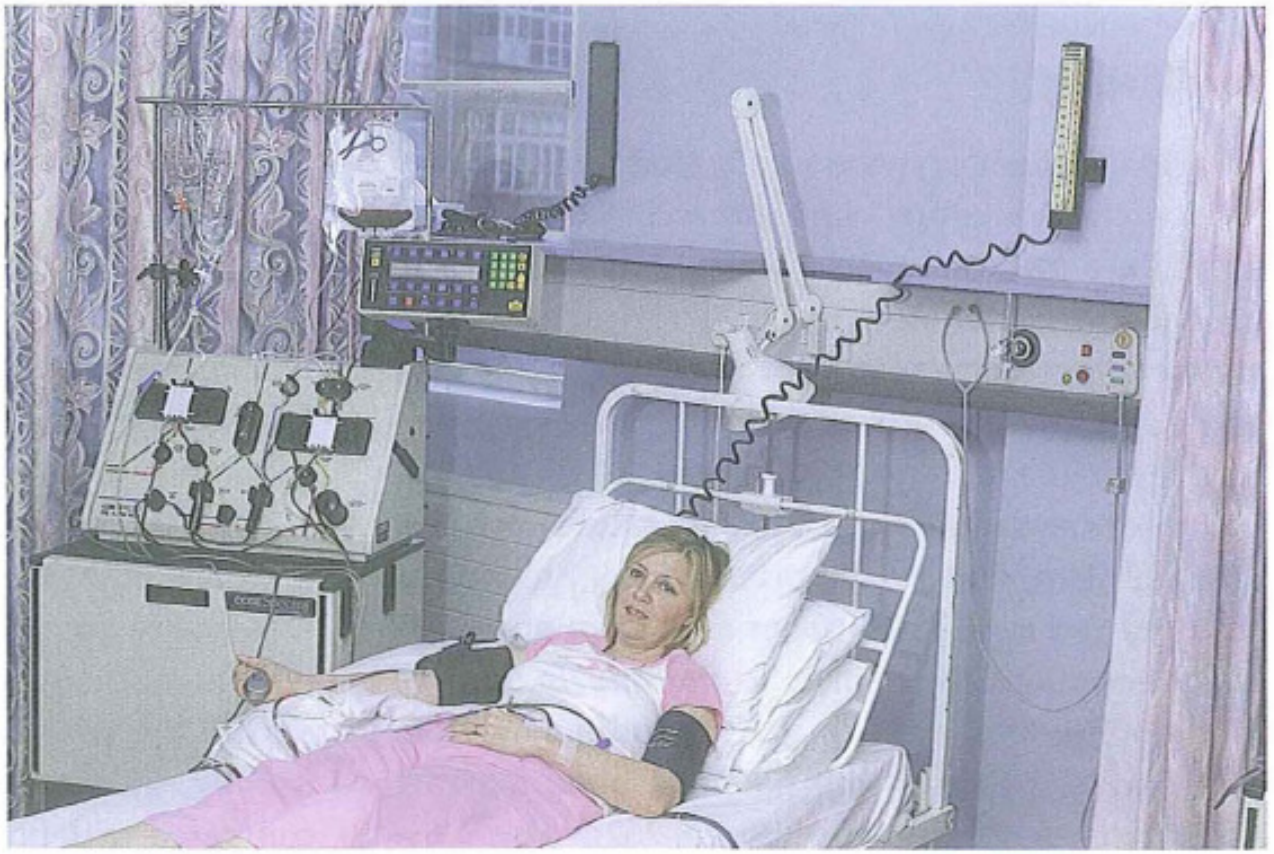
2- Peripheral blood:

- The term *peripheral blood stem cell* (PBSC) *transplantation* is used if HSCs were mobilised to the peripheral blood using G-CSF.

3- Cord blood:

- human umbilical cord blood stem cells can be used for children and small adults.

Collection of mobilised PBSC



Allogeneic stem cell transplantation

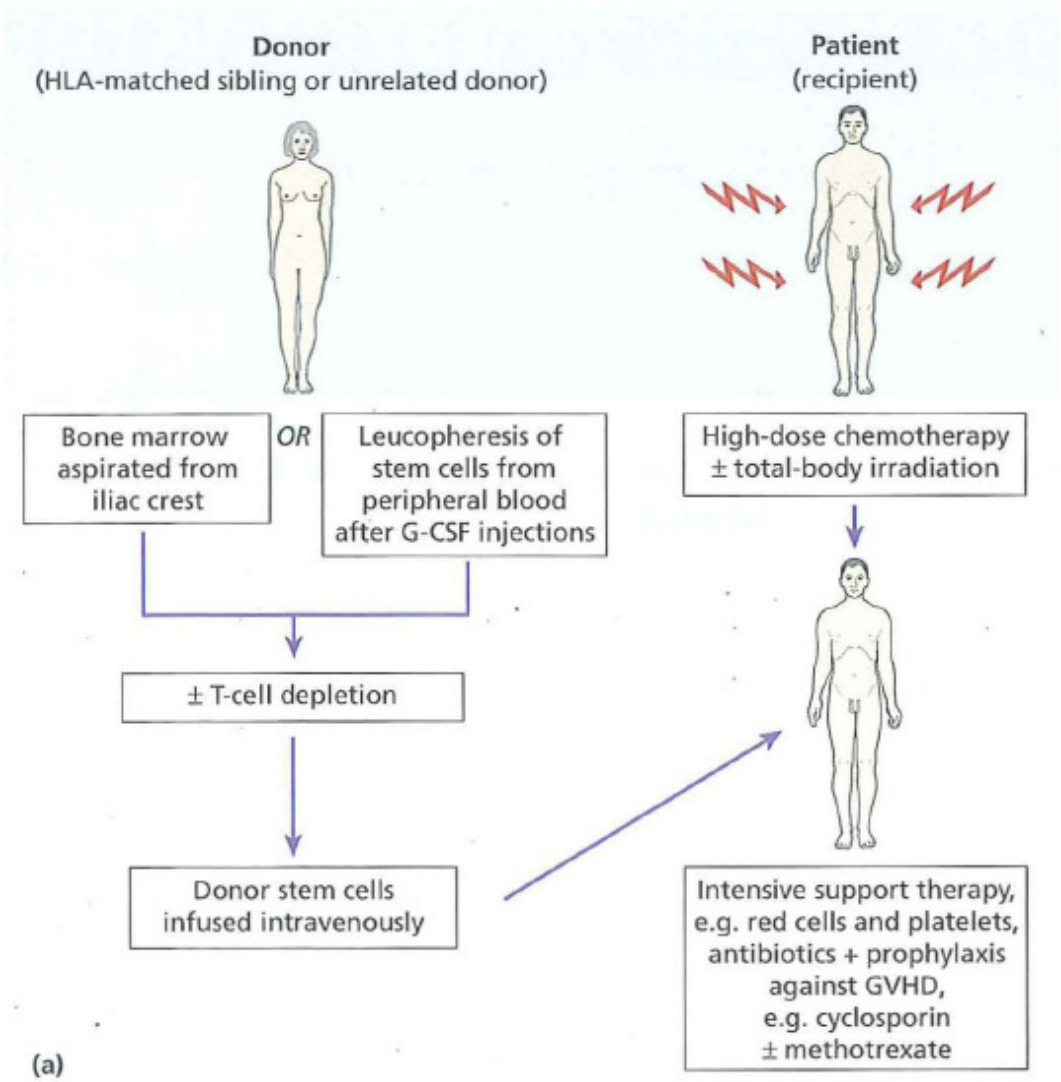
- In this procedure, stem cells harvested from another person are infused into the patient.

- The procedure has a significant morbidity and mortality.
- Reasons: is the immunological incompatibility between donor and patient despite matching of the human leucocyte antigens (HLA).

- This may manifest as imnunodeficiency, GVHD or graft failure.

- Paradoxically, there is also a graft-versus leukaemia (GVL) effect which probably underlies much of the success of the procedure.

Allogeneic SCT



Autologous stem cell transplantation

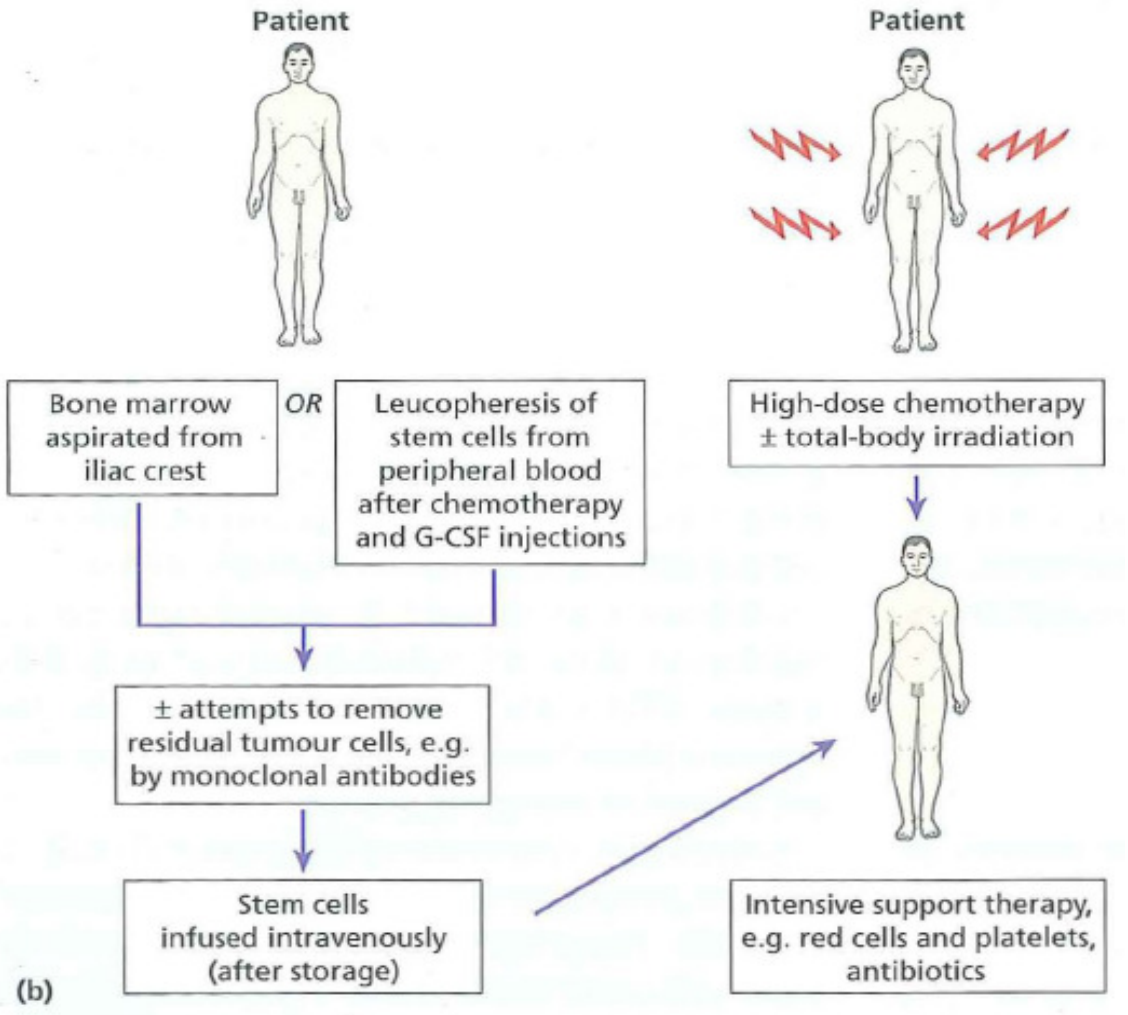
- Patient undergos a high dose of chemotherapy, with or without radiotherapy.
- Stem cells are harvested and stored before the treatment is given and are then reinfused to 'rescue' the patient from the myeloablative effects of the treatment.

- A limitation of the procedure is that tumour cells contaminating the stem cell harvest may be reintroduced into the patient.

- Autografting has a major role in the treatment of haematological diseases such as lymphoma and myeloma and is under investigation in other diseases such as acute leukaemia and severe autoimmlme diseases.

- Major advantage is avoidance of GVHD.
- Major problem is recurrence of the original disease.

Autologous SCT



Indications for allogeneic SCT

- Acute lymphoblastic or myeloid leukaemia
- Chronic myeloid leukaemia
- Other malignant disorders of the marrow (e,g, myelodysplasia, multiple myeloma, lymphoma, chronic lymphocytic leukaemia)
- Severe aplastic anaemia including Fanconi's anaemia
- Inherited disorders: thalassaemia major, sickle cell anaemia, immune deficiencies, inborn errors of metabolism in the haemopoietic and mesenchymal system (e.g. osteopetrosis)
- Other acquired severe marrow diseases (e.g, paroxysmal nocturnal haemoglobinuria, red cell aplasia, myelofibrosis)

Indications for autologous SCT

- Hodgkin's lymphoma and non-Hodgkin's lymphoma
- Multiple myeloma
- Acute and chronic leukaemias
- Severe autoimmune disease
- Amyloidosis
- Gene therapy of genetic disease (e.g. adenosine deaminase deficiency).

Collection of stem cells

- **Bone marrow collection**
- The donor is given a general anaesthetic and 500-1200 ml of marrow is harvested from the pelvis.
- The marrow is heparinized and a mononuclear cell count is taken to assess the yield (2-4 x 10^8 nucleated cells/kg bodyweight of the recipient).
- **Peripheral blood stem cell collection**

-(G-CSF) is given to patients or donors as a course of injections

(typically 10 µg/kg/ day for 4-6 days) until the WBC count starts to rise.

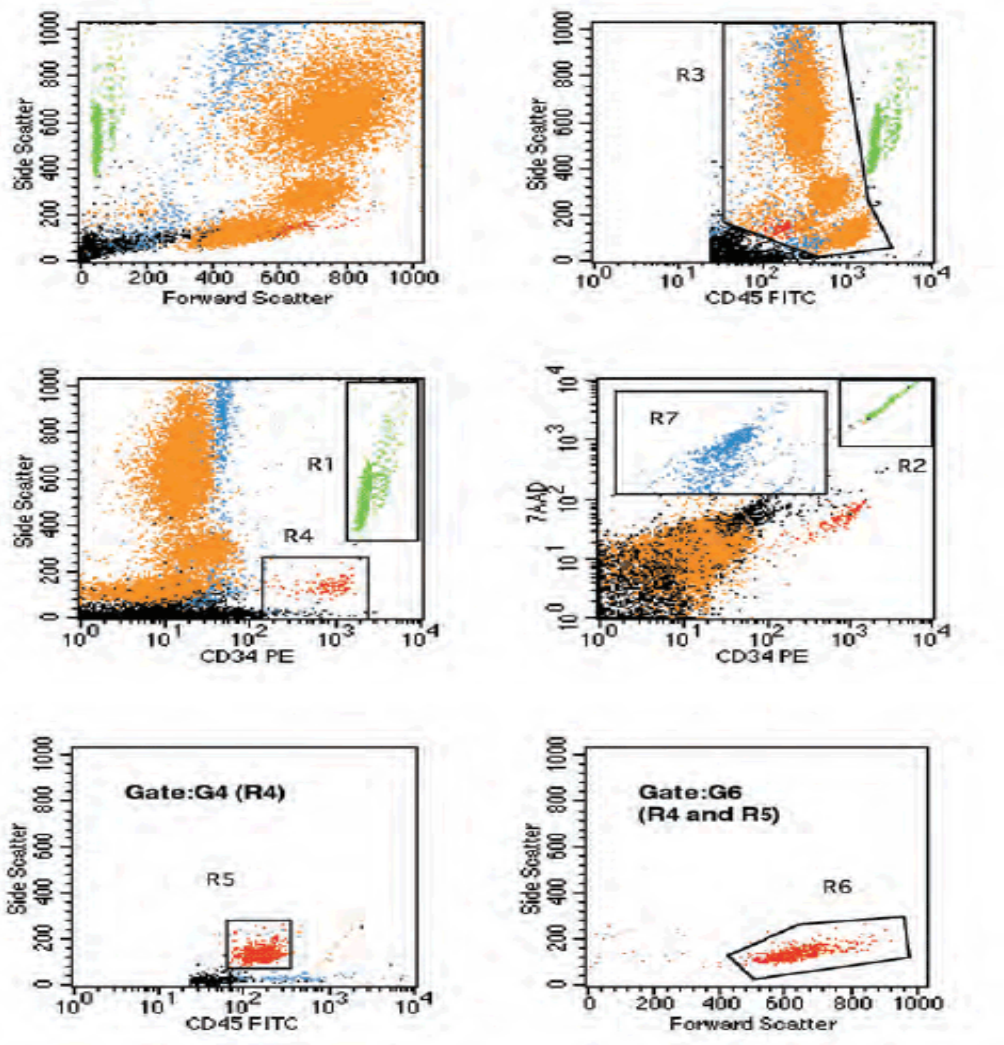
-PBSC collections are taken by leucopheresis and the yield is assessed.

- Process can be repeated.

-Chemotherapy and growth factors can each increase the HSC number by around 100 times.

✓ CD34+ cells in the collection are counted using flow cytometry.

✓ >2.5 x 10^6/kg are needed for autologous transplantation.



Gate: No Gate
Gated Events: 105832
Total Events: 105832

Gate	Events	% Total
CD34+ cells	529	0.50
CD45+ cells	70707	66.81
beads	7074	6.68
dead cells	4490	4.24
G4	971	0.92
G5	2643	2.50
G6	538	0.51

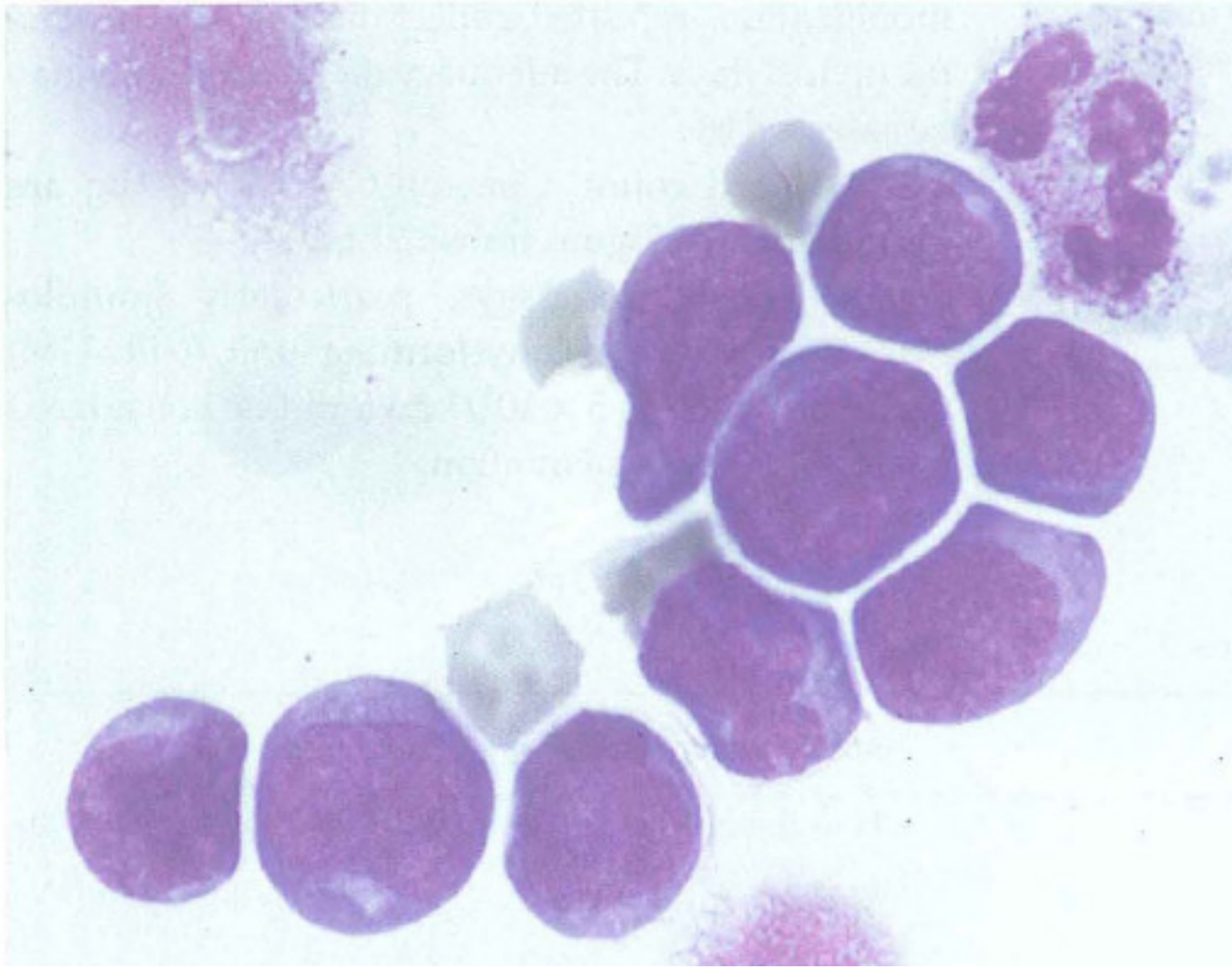
Stem cell processing

1- Stem cell harvest is processed with removal of red cells and concentration of the mononuclear cells.

2- Autologous collections may be 'purged' by chemotherapy or antibodies in an attempt to remove residual malignant cells.

3- Allogeneic collections may be treated with antibodies to remove T cells to reduce graft-versus-host disease (GVHD).

4- Enrichment of CD34+ cells (selection) before transplantation to enhance the engraftment.



Conditioning

1- Patients receive chemotherapy, sometimes in combination with total body irradiation to get red of patient's haemopoietic and immune system as well as malignancy.

2- This is essential in allogeneic SCT to prevent rejection of donor stem cells by patient immune system.

3- Current practice on SCT use *non-myeloablative* conditioning instead of *myeloablative* conditioning regimes.

** Non-myeloabalative conditioning does not completely ablate the patient's bone marrow.

Mini-transplants

- Non-myeloablative conditioning (mini-transplants) consists of administering lower doses of chemotherapy or radiotherapy followed by allogeneic bone marrow or peripheral blood stem cell administration to eradicate malignant cells.

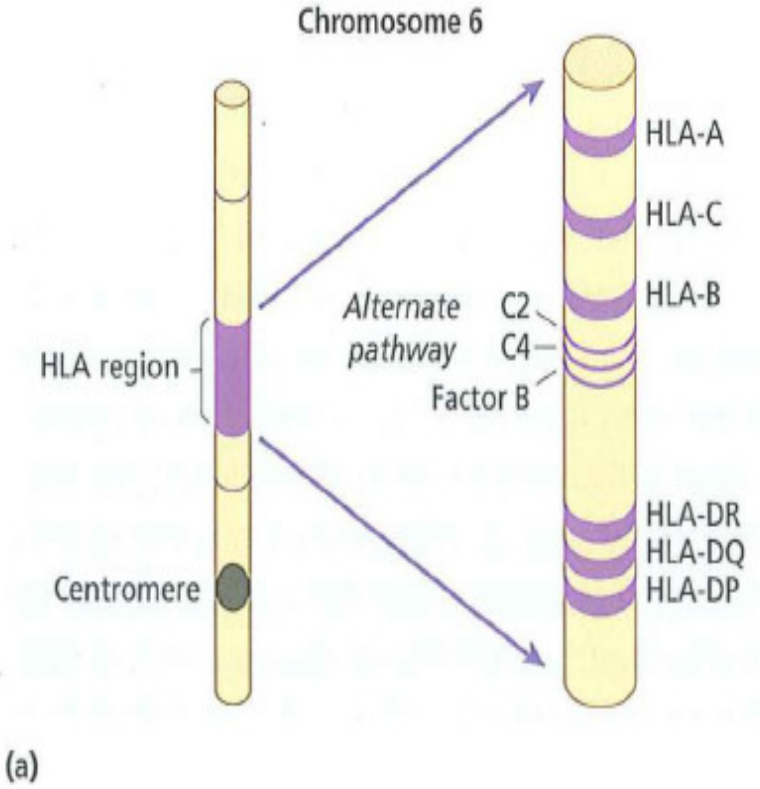
Post-transplant engraftment

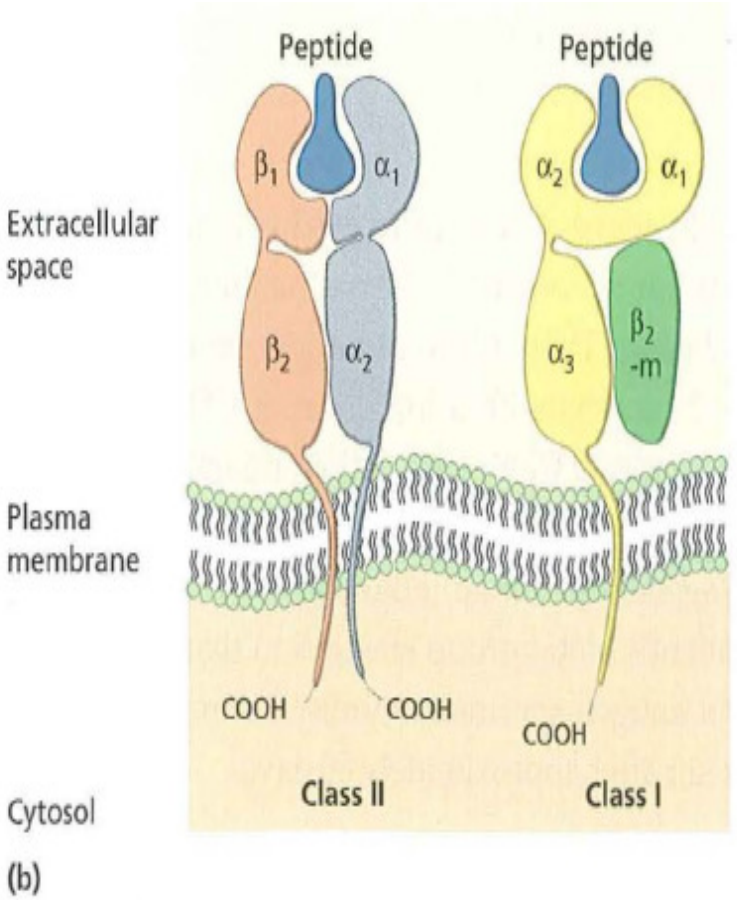
- First sign of successful engraftment is the appearance of monocytes and neutrophils in the blood with a subsequent increase in platelet count.
- Reticulocytes begins to appear in patient blood.
- Natural killer (NK) cells are among the earliest donor-derived lymphocytes to appear.
- Engraftment is usually quicker following PBSC transplantation compared with BMT.
- Marrow cellularity gradually returns to normal.
- Immlmodeficiency remains for 3-12 months with a low level of CD4.
- Immune recovery is quicker after autologous and syngeneic SCT than following allogeneic SCT.
- The patient's blood group changes to that of the donor

Human leucocyte antigen (HLA) and transplantation

- Allografting would be impossible without the ability to perform HLA typing.
- chromosome 6 contains a cluster of genes known as the major histocompatibility complex (MHC) or the HLA region.
- These encode the HLA antigens.
- The role of HLA antigens is to bind intracellular peptides and 'present' these to T lymphocytes for antigen recognition.
- Class I molecules (HLA-A, -B and -C) present antigen to CD8+ T cells and class II molecules (HLA-DR, -DQ and -DP) present to CD4+ T cells.
- HLA molecules control T-lymphocyte responses and the greater the HLA mismatch the more severe is the immune response between transplanted cells

HLA antigens





HLA typing

- Serological.
- Flow cytometry.
- PCR

Complications of stem cell transplantation

Early (usually <100 days)	Late (usually >100 days)
Infections, especially bacterial, fungal, herpes simplex virus, CMV	Infections, especially varicella-zoster, capsulate bacteria
Haemorrhage	Chronic GVHD (arthritis, malabsorption, hepatitis, scleroderma, sicca syndrome, lichen planus, pulmonary disease, serous effusions)
Acute GVHD (skin, liver, gut)	Chronic pulmonary disease
Graft failure	Autoimmune disorders
Haemorrhagic cystitis	Cataract
Interstitial pneumonitis	Infertility
Others: veno-occlusive disease, cardiac failure	Second malignancies

Complications of stem cell transplantation

- Graft-versus-host disease

- donor-derived immune cells, particularly T lymphocytes, reacting against recipient tissue.

- Further reading about GVHD is required!!

Erythematous skin rash in acute GVHD