Transfusion in transplantations

CLS 542

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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.

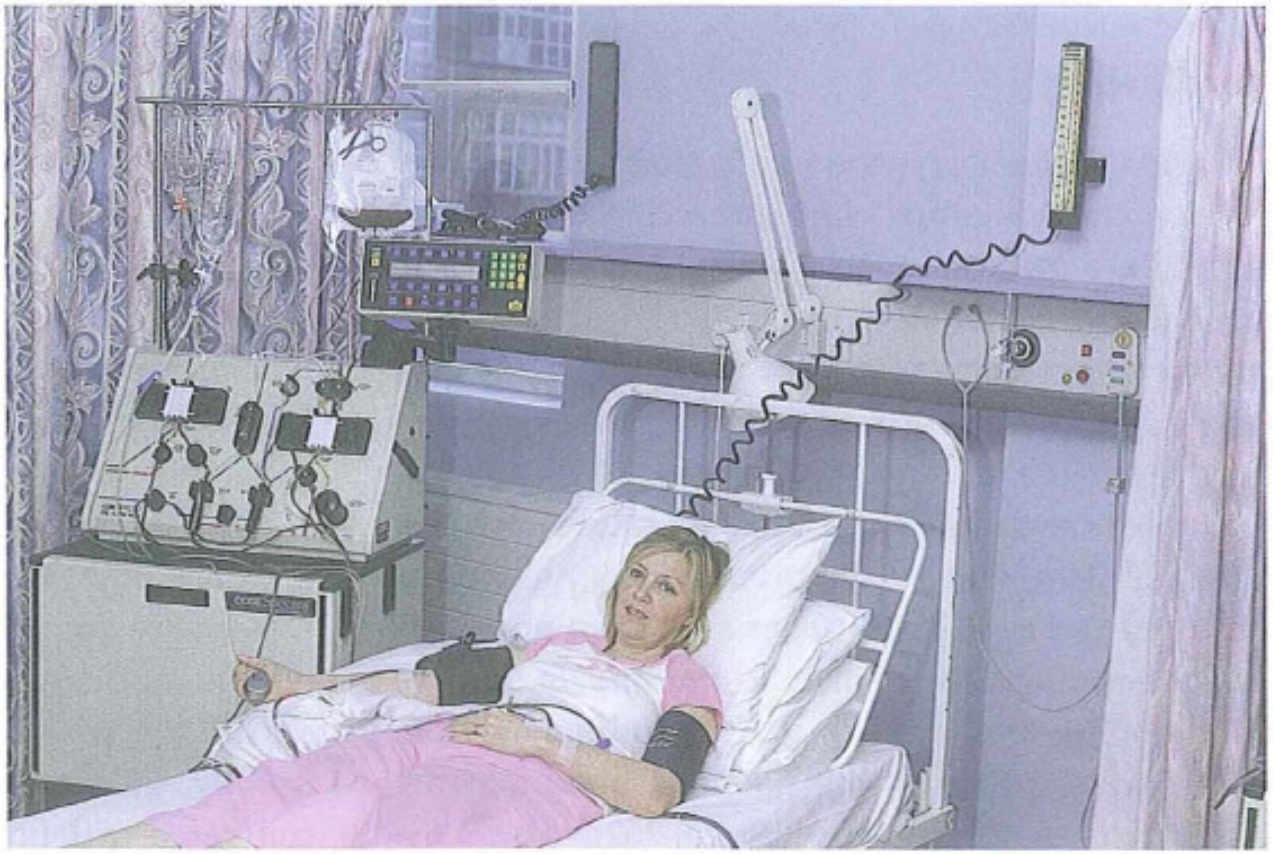
2- Peripheral blood:

- The term *peripheral blood stem cell* (PBSC) *transplantation* is used if HSCs were mobilised to the peripheral blood using G-CSF.
- The donor is given G-CSF for 4-5 days to mobilise the Bone marrow stem cells into the peripheral blood.
- Collection of PB is accomplished in 1-2 days by leukopheresis.

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

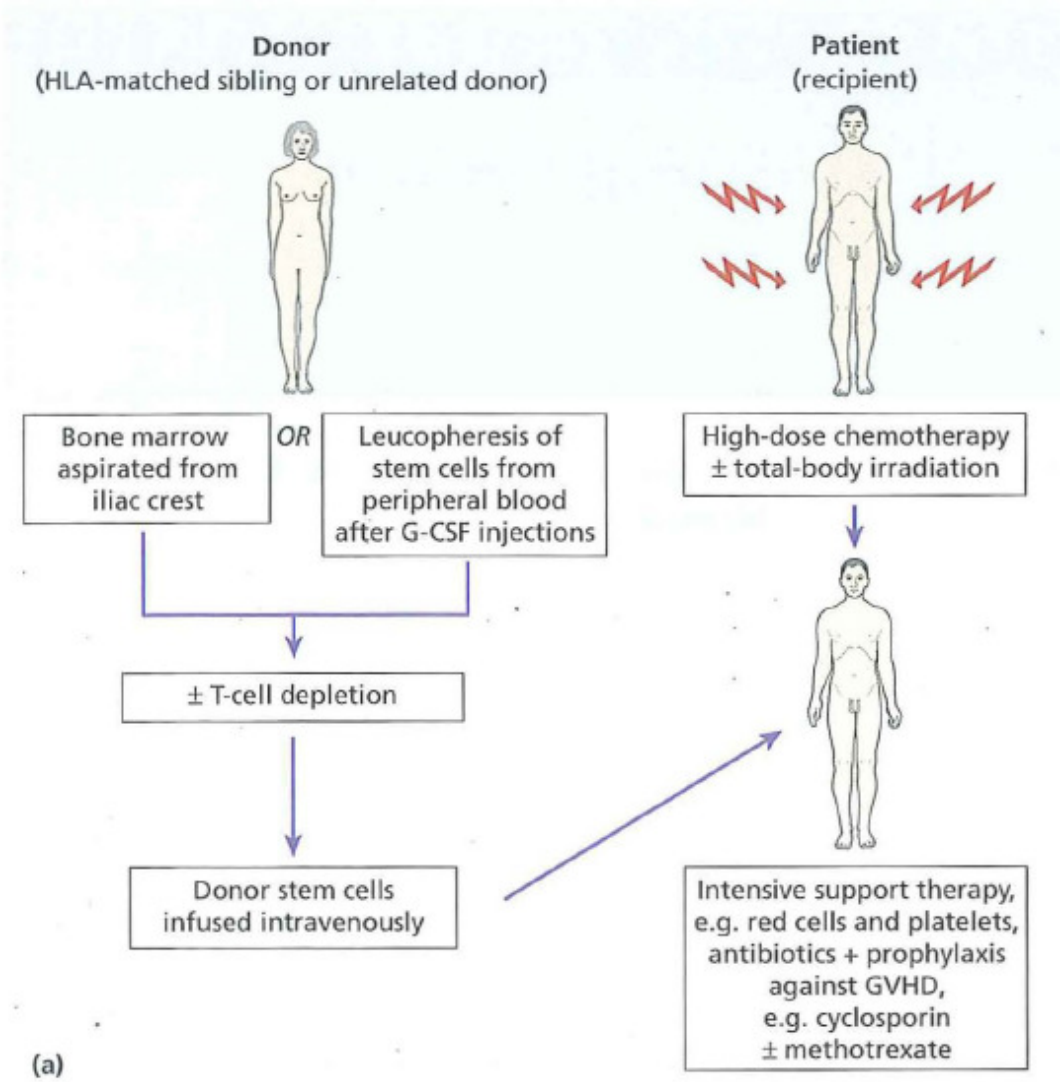
- In this procedure, stem cells harvested from another person are infused into the patient.

- 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

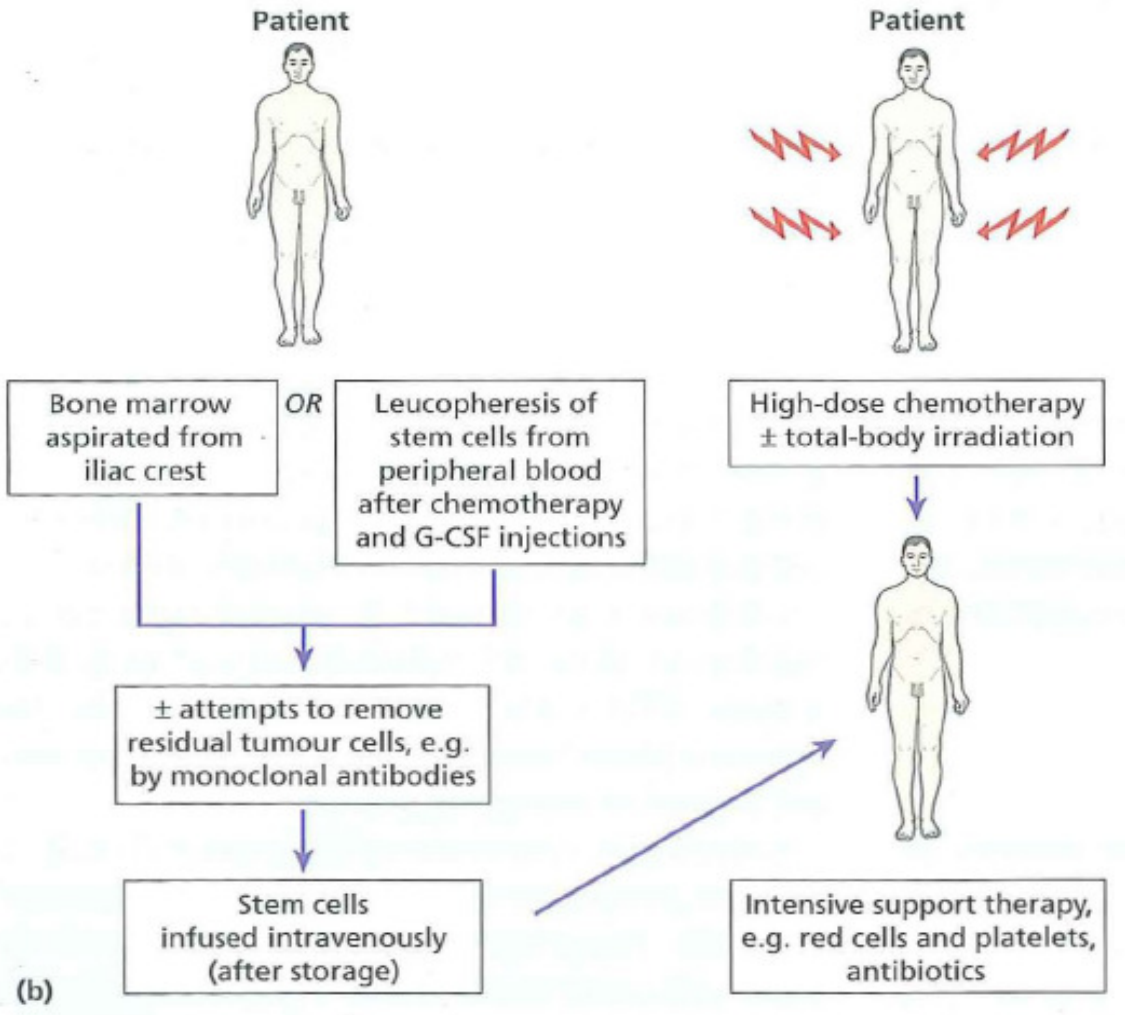
- Patient undergos a high dose of chemotherapy, with or without radiotherapy.
- Stem cells are harvested and stored before the treatment is given and are then reinfused to 'rescue' the patient from the myeloablative effects of the treatment.

- 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.

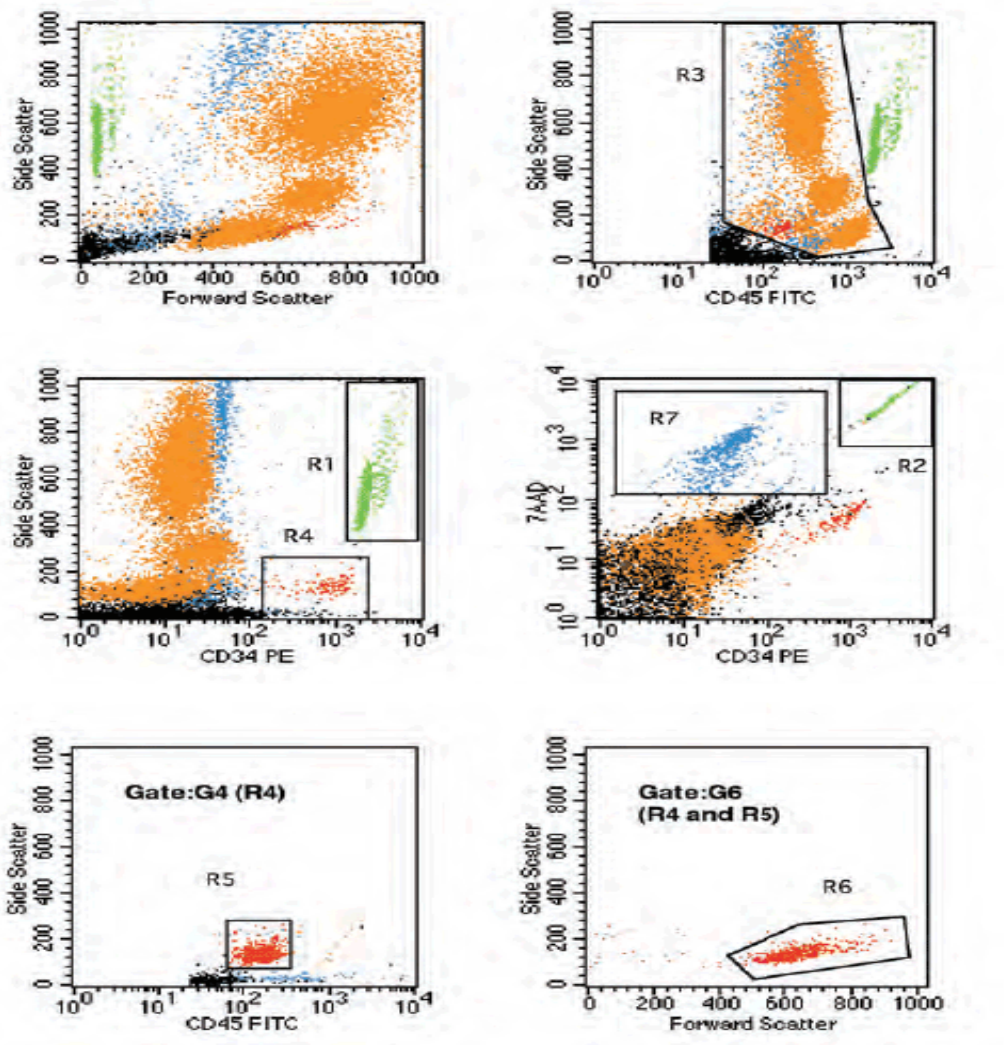
-PBSC collections are taken by leucopheresis and the yield is assessed.

- 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- ***In ABO incompatible bone marrow***, the plasma or RBCs may be reduced to lessen haemolytic transfusion reaction when the bone marrow is infused.

5- 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.
- Immunodeficiency 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 leukocyte 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

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

Special considerations for transfusion in HSC transplantation

- patients will require blood transfusions for weeks or months post-transplantation (support therapy).

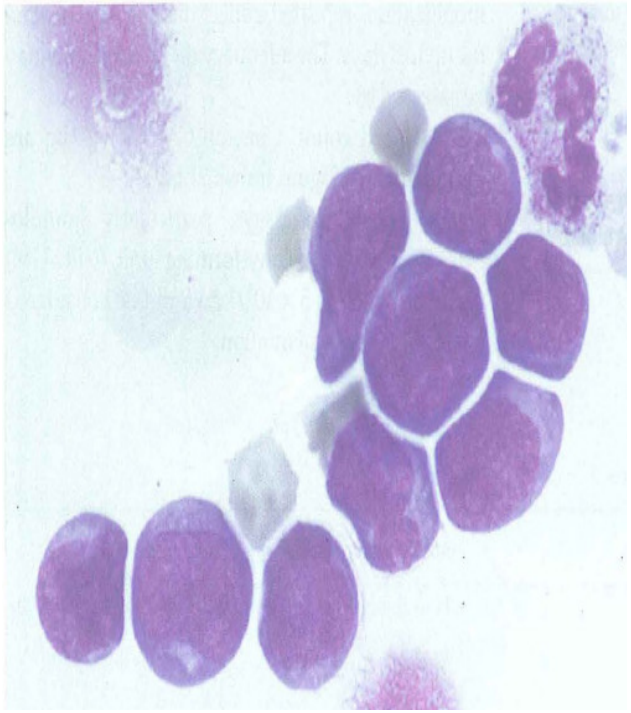
1- RBC and platelets products must be ***irradiated*** to prevent ***GVHD*** in recipient of HSC transplantation.

2- CMV-negative recipients must receive leukodepleted or CMV negative transfusions.

3- platelets may need to be cross-matched and/ or HLA-matched in case of platelets refractoriness.

4- RBC, FFP, and platelets units that are used in transfusion should be compatible for both the donor and the recipient!! ***See case study 4 in Ch16.***

Transfusion in HSC transplantation



-Bone marrow or peripheral blood stem cell products can be infused fresh, stored at RT for 24h, or cryopreserved in liquid nitrogen.

- Major ABO incompatibility (patient's circulating ABO antibodies) may cause haemolysis of the donor RBCs and **delay engraftment** of the erythropoietic line.

-Minor ABO incompatibility may result in haemolysis of patient RBCs by donor's ABO antibodies (Solution: remove plasma from donor BM).

- If cord blood is used as a source: ABO, Rh, and HLA type must be determined on the infant, and the RBC antibody screen is performed on the mother blood.

ABO mismatched HSC transplants

- An HLA-matched donor is commonly of a blood group different from that of the recipient.
- Appropriate measures must be taken to avoid acute or delayed hemolytic reactions during transplantation involving either minor or major incompatibility.
- ***Minor ABO incompatibility*** means that the donor possesses anti-A and/or anti-B capable of reacting with A and/or B antigens on the recipient's red cells and tissues. (group A recipient and group O donor).
- Platelets and FFP of the ***recipient blood group*** should be given before and after the chemotherapy until the disappearance of recipient circulating RBCs.
- ***Major ABO incompatibility*** occurs when the recipient possesses anti-A and/or anti-B capable of reacting with ABO antigens on donor red cells (e.g, group O recipient and A donor).
- Only RBCs of the recipient's ABO group should be transfused as long as anti-A and/or anti-B are detectable.
- Platelets and FFP should be switched to the donor's ABO type to avoid transfusion of large volumes of incompatible anti-A and/or anti-B that would destroy RBCs of the donor type.

ABO mismatched HSC transplants

- As the HSC engraft, the recipient will slowly become the donor's ABO group.
- ***Example: if the HSC donor is group A and the patient is group O?***
- The anti-A antibodies in patient plasma will become weaker several weeks after HSC transplant, and eventually will dissapear.
- After few months, group A RBCs will appears as mixed field.
- Eventually, the recipient will type as group A.
- **Remember:** transfusing the blood group of choice of blood components for both the donor and the recipient is extremely important in post HSC transplantation settings. (See case study 4).
- However, in many cases, RBCs and platelets/plasma will have different preferred ABO blood groups.
- **Example:** in case HLA-matched platelets are required, the preferred ABO group may not be available➔ ABO mismatch between donor and recipient.

Solid organ transplantation

- ABO compatibility is essential to organ transplantation.
- Major ABO incompatibility may cause death of the transplanted organ.
- Liver transplant requires the most transfusion support (10-20 units of RBCs and FFP).
- Because of the massive transfusion required in liver transplant:

1- The ABO type of RBCs may need to be switched (see table 16-11).

2- The Rh-negative type of patient may need to be disregarded.

Transfusion in oncology

- Oncology patients may need supportive therapy for long periods.
- Repeated RBC and platelets transfusions may lead to the need for rare RBC units and or HLA-matched platelets.
- Platelets use may require a change from Rh-negative to Rh-positive products. In this case, 300 µg dose of Rh-Ig may be given to women at child-bearing age to protect against immunization.
- Certain oncology patients (CLL, Lymphoma, etc) have increased destruction of RBCs and may cause pre-transfusion testing problems.
- Lymphoma and HD patients are at increased risk of ***GVHD*** and should receive ***irradiated*** blood components.

Useful resources

- http://www.ortho-wire.com/en/
- Modern blood banking and transfusion practice (text book). Ch16.
- http://www.clinlabnavigator.com/transfusion/abomismatched.html