Recipient & Transplantation

· Hematopoiesis:

Hematopoietic stem cells (HSC) = pluripotent cells:

- --> Myeloid stem cell → erythrocytes, platelets, leukocytes, dendritic cells, macrophages
- --> Lymphoid stem cell → T cells, B cells

Type of HSC transplant

Autologous, allogeneic, syngeneic

Stages of HSCT

Decision to treat, donor search, conditioning, transplantation, reconstitution of hematopoiesis

Indications

Hematological malignancies (leukemia's and lymphomas), primary immune deficiencies and inherited or acquired bone marrow deficiencies (such as severe forms of thalassemia or severe aplastic anemia). Example: Chronic myeloid leukemia (CML): transformation of early pluripotent stem cell

- Myeloproliferative disorder due to a translocation between chromosome 9 and 22
 --> Philadelphia (Ph) chromosome
- The ensuing gene (BCR-ABL) encodes kinase protein with a deregulated activity
 BCR ABL activity is inactivated by Glivec. Drugs are palliative, only an allogeneic HSCT is able to cure CML.

Decision to treat

Risk-evaluation of mortality/morbidity and expected quality of life, comparison with other therapies Factors arguing for HSCT: availability of matched donor, young age, early stage of disease, ...

• Conditioning (before transplantation)

High dose chemotherapy (cyclophosphamide) and/or total body irradiation (TBI)

- --> Destroys the patient's HSC (myeloablative effect)
- --> Creates space for the transplanted donor HSC
- --> Prevent from graft rejection (patient's immune system destroyed)

--> high risk of infections (antibiotic prophylactically, sterile environment)

Main problem: organ toxicity

<u>Alternative: Non myeloablative conditioning</u> (increasingly prescribed because of its lower toxicity)

- --> Does not destroy hematopoiesis
- --> With time, donor T cells destroy the hematopoiesis of the recipient including residual leukemic cells (GVL)

Transplantation

Infusion of donor HSC (marrow or PBSC), migration of HSC to patient's bone marrow, production of all cell lineages (graft take) after 7-20 days, delayed production of T and B cells CD34: cell surface molecule (marker for HSC)

Donor & Compatibility

- Criteria
 - HLA typing
- Search
- Stem cell source

Transplantation barriers

- Structures recognized
 - •MHC
 - •mHC
- Allorecognition
 - T cells
 - •B cells
 - NK cells

Immunosuppression

- Immunosuppressive drugs
- T cell depletion

Complications

- Graft rejection
- GVHD
- Infections
- Side effects
- Relapse

Reconstitution

- Engraftment
- Myeloid cells
- T cells
- B cells
- Chimerism

LEARNING OBJECTIVES

- Hematopoietic stem cells
- The role of bcr-abl (translocation) in the pathogenesis of CML. Working mechanism of the drug targeting bcr-abl