Bone Marrow Transplantation

Hematopoietic Stem Cell Transplantation

overview

- Chemotherapy → infusion hematopoietic stem cell
- Treat disease, restore no
- rmal hematopoiesis
- Bone marrow → multipotent stem cells and postthymic lymphocytes
- Autologous HCT → rescue the bone marrow

overview

- Preparative or conditioning regimen (higher doses)
- To eradicate the residual malignancy, suppress the recipient's immunity
- ***Autologous HCT*** → myeloablative preparative regimen
- ***Allogeneic HCT*** → myeloablative, reduced intensity

overview

- Period of pancytopenia until infused HSC re-establish functional hematopoiesis (engraftment)
- Engraftment : sustained ANC > 500cells / µL and platelet count of at least 20000/ µL lasting three consecutive days without transfusions

Sources of HSC

- Peripheral blood progenitor cell transplant (PBPCT)
- Bone marrow transplant (BMT)
- Umbilical cord transplant (UCT)

Autologous HSCT

- Donor and recipient are the same
- Pretransplant and posttransplant immunosuppression is unnecessary
- Stem cells obtained before preparative regimen
- Rescue to re-establish bone marrow function
- Main cause of relapse → incomplete tumor eradication
- Nearly all pts have failed standard chemotherapy regimen

Autologous HSC

- PBPCs → main source (up to five times more HSC)
- More rapid engraftment → fewer days of neutropenia

Mobilization and collection of autologous PBPCs

- low number of PBPCs in peripheral circulation
- G-CSF (filgrastim) : 10-24 mcg/kg/day SC
- CD34+ cells → hematopoietic multipotent cells

Plerixafor (new agent)

- CXCR4 inhibitor → blocks SDF-1 from binding to CXCR receptor → remains in blood circulation

- SDF-1 , a chemo attractant agent for HSC → causing rapid HSC migration to peripheral blood

Characteristics of stem cells

- # of cells expressing CD34 antigen → most reliable indicator of adequate PBPC collection
- Minimum of 1-3 X 10^6 CD34+ cells/kg of recipient weight
- ≥5-8 X 10^6 cells/kg → more rapid engraftment

Complications of autologous HCT

- Infection and organ failure (<5% of pts)
- No profound immunosuppression or GVHD
- outpatient care
- Profound aplasia due to myeloablation preparative regimen
- Growth factors

Allogeneic HSCT

Histocompatibility

- 1- cytotoxic T cells and NK cells of host recognize MHC antigens of the graft → graft rejection
- 2- immunologically active cells in graft recognize host MHC antigens → GVHD

➢ HLA- compatible graft

Histocompatibility

- Siblings → most likely to be histocompatible
- Class 1 MHC antigen (HLA-A, HLA-B, HLA-C)
- Class 2 MHC (HLA-DR, HLA-DP, HLA-DQ)
- Most important alleles to match → HLA-A, HLA-B, HLA-C, and HLA-DRB1
- Haploidentical donors: parent, sibling, child
- Normal renal, hepatic, pulmonary, and cardiac functions
- Patients up to 65 years old

Transplanting allogeneic HSCs

Bone marrow

- Surgical procedure
- Posterior iliac crest
- Primary source for allogeneic transplant in children (60%)

Peripheral blood

- 4-5 days of G-CSF → pheresis on 4th or 5th day → 4-10 X 10 6 cells/kg of recipient weight
- Donor SE: musculoskeletal pain, headache, mild increase in hepatic enzyme or lactate dehydrogenase and hypocalcemia
- Similar incidence of acute GVHD as bone marrow but 20% higher incidence of chronic GVHD

UCB

- Rich in HSC
- Limited in volume

Chimerism

- Detection of donor–derived and recipient–derived hematopoietic cells
- Mixed chimerism (5-95% donor T cells present in recipient peripheral blood)
- Assessed within T cells and granulocytes in the peripheral blood and bone marrow
- Opposite sex donors → using sex chromosomes
- Same sex donors → molecular
- DLI : donor lymphocyte infusion → to augment the GVT activity

Posttransplant immunosuppressive therapy

- Cyclosporine or tacrolimus + low dose MTX
- Corticosteroids → more commonly for treatment of GVHD
- Slowly tapered and discontinued over the course of 6 months to one year due to immunologic tolerance

Complications associated with HSCT

Busulfan seizures

- 10% of patients
- Highly lipophilic
- CSF:plasma ratio of 1 or higher
- Direct neurotoxic effect
- Seizure prophylaxis: starting 12 hrs before the first busulfan dose and usually discontinued 24-48 hrs after the last dose

Hemorrhagic cystitis

- Cyclophosphamide , acrolein
- Mesna → donates free thiol groups to bind acrolein
- ASCO → mesna + saline diuresis

Chemotherapy induced GI effects

- 1- CINV: serotonin antagonist (granisetron) plus corticosteroid
- ASCO guidelines: neurokinin receptor 1 antagonist, aprepitant

- 2- mucositis , MTX also contribute to mucositis

Myelosuppression and growth factor

- ASCO guideline: in allogeneic PBPC is controversial
- Decrease the duration of neutropenia
- Does not decrease the cost , length of hospitalization, or antibiotic use
- May increase the incidence of severe GVHD and lower survival

GVHD

- Activation of donor lymphocyte
- Most important complication of allogeneic HCT
- Causes: 1- the preparative regimen results in tissue damage and release of inflammatory cytokines into circulation
- 2- recipient and donor antigen presenting cells and inflammatory cytokines trigger activation of donor- T cells
- 3- the activated donor T cells cause tissue damage

Acute GVHD

- The first 100 days after allogeneic HCT
- Damage skin, GI tract, liver
- Grade II-IV acute GVHD → 20-50% of HLA-matched sibling grafts; 50-80% of HLA-mismatched sibling or HLA-identical unrelated donors
- Other risk factors: ↑recipient (possibly donor) age, greater intensity of preparative regimen, use of PBPC, donor/recipient sex mismatch

Immunosuppressive prophylaxis

- 1- cyclosporine + short course MTX
- 2- tacrolimus + short course MTX
- Two drugs with different mechanism, 1-CSA blocking the activation of T cells , 2-MTX blocking the division and clonal expansion of activated T cells

Cyclosporine

- Inhibit production of helper T-cell derived IL-2 → block proliferation of cytotoxic T cells
- Initially administered IV due to GI effects of preparative regimen
- IV to PO → 1:2 or 1:3
- Tacrolimus → 1:4
- Dose of CSA and tacrolimus adjusted based on serum drug levels and SCr
- Doses ↓by 50% if SCr doubles above baseline and hold if SCr >2mg/dL

Treatment of established acute GVHD

- First line treatment → corticosteroid added to current regimen
- Block macrophage – derived IL-1 secretion
- IL-1 is a primary stimulus for helper T-cell induced secretion of IL-2 , which is responsible for stimulating proliferation of cytotoxic T lymphocytes
- Methylprednisolone : 1-2 mg/kg/day

Chronic GVHD

- Most common late complication of HCT
- Major cause of nonrelapse morbidity and mortality
- Non-modifiable risk factors: older age, certain diagnosis (CML), lack of an HLA-matched donor
- Modifiable factors: selecting younger donor, avoiding a multiparous female donor, using UCB or BM graft rather than PBPC, limiting the CD34+ and T-cell dose infused
- 70-80% of pts with grade II to IV acute GVHD → chronic GVHD

Pharmacologic management

- No prophylactic therapy
- Long – term immunosuppressive therapy
- Typical regimen : prednisone 1mg/kg /day

Infectious complications

- Antibacterials
- Antifungals
- antivirals