Introduction

Major Complication of Allogeneic Stem Cell Transplantation
Impediment to cure
Acute Graft versus Host Disease (aGVHD)
Chronic Graft versus Host Disease (cGVHD)

Requirements for Induction of aGVHD
- Immunologically Competent Cells
- T Cells
- Foreign Host
- Host Immune system unable to respond

Principles of Pathophysiology
- Not a disease per se
  - Normal physiologic response
- Profound Damage to host
  - Underlying disease
  - Prior infections
  - Intensity of condition regimen
  - Proliferation of Inflammatory Cells
- Expression of adhesion molecules
- Cytokines
- Co-stimulatory molecules

3 Sequential Phases
- 1) Conditioning Regimen
- 2) Donor T Cell Activation (afferent phase)
- 3) Effector Phase (efferent phase)
  - Amplification of signals

Slide not available
Genetic Basis
- Major Histocompatibility Complex
- Human Lymphocyte Antigen (HLA) region
- Class I: HLA A, B, and C
- Class II: HLA Dr, DQ and DP
- Haplotypes

Determining HLA types
- Haplotypes
- Related and unrelated matches
- Homogenous populations
- Polymorphism

Conditioning Regimen
- Total Body Irradiation
- Myeloablative chemotherapy eradicate residual disease ablates host immune response creates space
  Very Toxic to the Gut

Gut Toxicity
- Increases gut permeability
- Loss of water and ions into intestinal lumens
- Translocation of bacterial derived products into the circulation
- Release of proinflammatory cytokines including Tumor Necrosis Factor alpha and IL 12 from host tissues

Inflammatory Cytokines
- Central Regulatory molecules of the immune system
- Activation of antigen presenting cells (APC) that amplify graft derived T cells
- Increases MHC antigen expression

Donor T Cell Activation
- Donor T cell interaction with host antigen presenting cells (APC)
- MHC disparity presenting peptides
- The greater the disparity; the greater the T cell response
- Co-Stimulatory signals
- Anergy or tolerance
**Effector Phase**
- Complex Cascade
- Cellular Effectors: cytotoxic T cells and NK cells
- Inflammatory Effectors: TNF and IL1
- Amplification of local tissue injury
  - Epithelial damage of target organs
- Positive Inflammatory response feedback loop

**Prevention and Treatment**
- Non Specific immunosuppressive drugs
- T Cell Specific
- Antibodies
- Anti-cytokines
- Novel agents

**Cyclosporine**
- Calcineurin Inhibitor
- IL-2 production is inhibited
- Tcell activation is prevented
- Leads to disruption of PH III (effectors) by decreasing activated CTLs, NK cells and monocytes

**Cyclosporine**
- **Gold Standard** in combination with methotrexate for acute graft versus host disease prophylaxis and with steroids for chronic graft versus host disease treatment.
- Fred Hutchinson Experience (1988), Sullivan, KM et al.
- Dosing/Side effect profile/Nursing implications.

**Methotrexate**
- Antimetabolite with selective inhibition of the proliferation of T and B lymphocytes by interfering with purine nucleotide synthesis.
- Gold standard with CSA for acute GVHD prophylaxis.
- Institutional variability for schedules and dosing.
- Dosing/Side effect profile/Nursing implications

**Corticosteroids**
- Lympholytic agents
- Inhibit the release of inflammatory cytokines such as IL-1, IL-2, IL-6, interferon gamma, and tumor necrosis factor.
- Historic gold standard for treatment of acute and chronic GVHD.
- Long term salvage rates for patients failing steroids have been < 20%.
- Fred Hutchinson and Minnesota experience.
- Dosing/Side effect profile/Nursing implications.
**Tacrolimus**
- Impairs synthesis of IL-2 which prevents T lymphocyte proliferation.
- Cytokine gene transcription interference (gamma interferon and alpha TNF).
- Replacing CSA in many centers.
- Utilized in prophylaxis regimens for aGVHD and treatment for cGVHD.

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**Sirolimus**
- Structurally similar to tacrolimus.
- Blocks IL-2 driven T cell proliferation and cell cycle arrest in Stage G1.
- Mechanism of action remains to be clarified.
- Macrolide

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**Mycophenolate Mofetil**
- Anti-proliferative drug that interrupts immune response signaling during DNA synthesis.
- Anti-metabolite
- Selectively inhibits the proliferation of T and B lymphocytes by interfering with purine nucleotide synthesis.

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**Tacrolimus**
- Acute GVHD Prophylaxis with MMF
  - University of Colorado, University of Nebraska, FHCRC, and the RMBMTP experience.
- Chronic GVHD Treatment
  - Kanamaru, A. et al. (1995)
- Dosing/Side effect profile/Nursing implications.

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**Sirolimus**
- Clinical trials evaluating the efficacy of treatment of acute and chronic GVHD.
- Animal models
  - Synergistic with co-stimulatory blockade in producing allograft tolerance.
  - 1 – 2 times more potent than CSA in preventing the rejection of vascularized allografts.
- Dosing/Side effect profile/Nursing Implications.

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**Mycophenolate Mofetil**
- Successful at preventing renal graft rejection.
- Acute GVHD prophylaxis
  - Bornhauser
- Treatment for acute and chronic GVHD
- Dosing/Side effect profile/Nursing Implications.
Antithymocyte Globulin
- Polyclonal immunoglobulin capable of destroying human lymphocytes,
- Horse/rabbit preparations
- Utilized in prophylaxis regimens, treatment for a GVHD and c GVHD.
- Swedish, FHCRC, Italian, and MD Anderson experiences.
- Dosing/Side effect profile/Nursing implications.

Alemtuzumab
- Monoclonal antibody directed against the cell surface antigen CD52 (expressed on T and B lymphocytes).
- Utilized in vivo and in vitro in acute GVHD prophylaxis.
  - Campath - 1M
  - Campath - 1G
- Hale (1998)
- Dosing/Side effects/Nursing Implications

Daclizumab
- Humanized monoclonal IgG1 antibody against IL-2 receptor expressed on activated T cells.
- Diminishes T cell activation.
- Clinical trials in GVHD prophylaxis
  - Przepiorka (2000)
- Dosing/Side effect profile/Nursing implications.

Visilizumab
- Humanized anti-CD3 monoclonal antibody.
- Selectively induces apoptosis in activated T cells.
- Dosing/Side effects/Nursing implications.

CTLA - 4 - Ig
- Blocks T cell co-stimulation through the B7 – CD28 interaction pathway.
- Tolerance inducing
- Minimizes global immunosuppression.
- Animal models blocking the B7-CD28 interaction inhibited both acute and chronic GVHD.
- Guinan clinical trial.
- Dosing/Side effect profile/Nursing implications.

PENTOSTATIN
- Leads to accumulation of dATP in lymphocytes which slows cell growth and causes cell death
- Decreases IL2 and TNF alpha production

PENTOSTATIN PROPHYLAXIS
NEW ENGLAND MEDICAL CENTER EXPERIENCE

- Reduced intensity regimen with extracorporeal photopheresis, pentostatin, reduced dose total body irradiation
- GVHD prophylaxis CSA/MTX
- Well tolerated
- Associated with low incidence of transplant related mortality
- Low incidence serious AGVHD and CGVHD


PENTOSTATIN PROPHYLAXIS
MDACC EXPERIENCE

- Dose escalation study
- Dose 1.5 mg/m2 days 8, 15, 22, 30
- GVHD prophylaxis FK506/MTX
- Decreased AGVHD
- Improved survival at day 100


PENTOSTATIN AGVHD
HOPKINS EXPERIENCE

- 22 patients evaluable
- 14 CR (64%)
- 3 PR (14%)
- 2 MR (9%)
- 3 PD (14%)
- In patients with grade IV there were 1 CR, 1PR, 1MR and only 1 NR


PENTOSTATIN CHRONIC GVHD
HOPKINS EXPERIENCE

- 41 patients evaluable
- 6 CR (15%)
- 14 PE (34%)
- 5 MR (12%)
- 16 PD (39%)

INFLIXIMAB/ETANERCEPT
CHILDREN'S HOSPITAL MEDICAL CENTER
CINCINNATI, OH

- Infliximab binds to TNF receptor, kills monocyte, more prolonged effect
- Etanercept blocks TNF receptor, effect temporary


INFLIXIMAB

- 24 pediatric patients, 16 with steroid refractory AGVHD
- Infliximab plus various other therapies
- Improvement 15/16 evaluable patients
  - 11/14 gut
  - 1/3 liver
  - 2/16 survivors

ETANERCEPT
UNIVERSITY MICHIGAN EXPERIENCE

- SQ twice weekly for up to 8 weeks
- 10/13 CR, most within 2 weeks
- CR more frequent for grade II than grade III AGVHD


ENTERACEPT (ENBREL)
SOUTH CAROLINA CANCER CENTER EXPERIENCE

- Steroid refractory AGVHD
- SQ twice weekly for 4 weeks then one weekly for 4 weeks
- 8/10 finished 8 week course
- 7/8 showed improvement

Steroid tapers started as early as 1 month


DENILEUKIN DIFTITOX (ONTAK)
DANA-FARBER EXPERIENCE

- Recombinant fusion protein (IL 2 fused to diphtheria toxin)
- Binds to IL-2 receptor leading to cytotoxicity against activate T cells
- 71% CR or PR in patients with steroid refractory AGVHD (n=24)
- 8/24 alive 6.3-24.6 months (median 7.2)


FUTURE DIRECTIONS

- NIH sponsored randomized 4-arm phase II study
- Goal is to identify a novel regimen suitable for subsequent phase III testing against corticosteroids alone
- Patients will receive corticosteroids plus:
  - Etanercept
  - MMF (CellCept)
  - Pentostatin
  - Denileukin difitox (Ontak)
- Group with highest response rate accrues the most patients.


EXTRACORPOREAL PHOTOPHERESIS (ECP)

- Expose lymphocytes to sensitizer and UVA irradiation in pheresis bowl
- Mechanism of selective immunologic effects poorly understood
- Multiple reports of its use as part of the conditioning regimen and treatment of CGVHD


ECP FUTURE DIRECTIONS

- Proposed international study of ECP for acute GVHD
- Continued studies trying to understand the mechanism of action.
Rituximab

- Anti-CD20 monoclonal antibody
- Depletes B-cells
- Evidence B-cell dysregulation might contribute to the pathogenesis of CGVHD


**RITUXIMAB UNIVERSITY OF MICHIGAN EXPERIENCE**

- Weekly IV at dose of 375 mg/m² for 4 weeks
- All patients received extensive prior treatment for CGVHD
- 4/8 patients responded despite recovery of B cells in 3 patients


**CYCLOPHOSPHAMIDE**

- High doses of cyclophosphamide ablate activated lymphocytes
- Used experimentally in autoimmune disorders (aplastic anemia, rheumatoid arthritis, lupus, scleroderma)


**FUTURE DIRECTIONS**

- Ongoing trials in auto-immune disorders
- Ongoing trials for GVHD prophylaxis in high risk mismatched transplants

GVHD

- More selective immunosuppression based on genotyping of key regulators in each patient-donor pair
- NIH consensus conference on Chronic GVHD, June 2005
  - Diagnosis
  - Staging
  - Response criteria
  - Clinical trial design
  - Supportive care
  - Biomarkers

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