Pharmaceuticals utilized in stem cell transplant

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Goals

- Review preparative regimens utilized in stem cell transplant
- Recognize the toxicities associated with agents utilized in the preparative regimen for blood and marrow transplant
- Identify pharmaceutical agents and their combinations, commonly used to prevent graft versus host disease
Ever-changing scene

- New pharmaceuticals introduced to the market
- New insights into disease management and transplant approach
- Improving patient outcomes
Preparative Regimens

- No regimen is suitable for all situations
  - Prior therapies/toxicities
  - Underlying organ dysfunction
- Usually begin 7-10 days prior to transplant
- Every regimen has its own toxicities
- Every center will have their own variations
Preparative Regimens

- Goal: To create “space” in the marrow without damaging other organs
  - Myeloablative (eliminating the host marrow)
  - Non-myeloablative (not completely eliminating the host marrow), more immunosuppressive than ablative to the marrow
Frequently used “ablative” preparative regimens in allogeneic transplants

- **Total body irradiation (TBI)** + Cyclophosphamide +/- Cytarabine (AraC)
- **TBI** + Cyclophosphamide +/− Etoposide (VP-16)
- Busulfan (PO or IV) + Cyclophosphamide
- Busulfan (PO or IV) + Fludarabine
Frequently used “non-ablative” preparative regimens in allogeneic transplants

- Fludarabine + Melphalan
- Busulfan + Cyclophosphamide (at lower doses)
- Busulfan + Fludarabine (at lower doses)
- TBI (reduced intensity) + Fludarabine
- Fludarabine + Cyclophosphamide
- More and more are evolving
Pharmaceuticals commonly used in autologous preparative regimens

- **Specific Agents**
  - Anthracyclines
  - Busulfan
  - Carmustine
  - Cyclophosphamide
  - Etoposide
  - Fludarabine
  - Melphalan
  - Monoclonal antibodies
  - Platinum derivatives
  - Thiotepa
Autologous Transplant Preparative Regimens

- Multiple myeloma
  - Mephalan
- Solid tumors
  - Carboplatin, cyclophosphamide, thiotepa, etoposide
- Autoimmune disorders
  - Melphalan
- Leukemia
  - TBI-based regimens
  - Busulfan/cyclophosphamide
- Lymphoma
  - TBI based
  - BEAM (carmustine, etoposide, cytarabine, melphalan)
Pharmacokinetics of major agents utilized in stem cell transplant

<table>
<thead>
<tr>
<th>Drug</th>
<th>Elimin. Route</th>
<th>Half-life</th>
<th>Normal Dose</th>
<th>SCT Dose</th>
<th>DLT</th>
<th>Common toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide (Cytoxan)</td>
<td>H/R</td>
<td>3-9 hrs</td>
<td>&lt; 1 gram/m²</td>
<td>4-8 gram/m²</td>
<td>Cardiac</td>
<td>Bladder, Hepatic</td>
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<tr>
<td>Thiotepa</td>
<td>H</td>
<td>30-120 min</td>
<td>65 mg/m²</td>
<td>400-1000 mg/m²</td>
<td>CNS</td>
<td>Mucositis, hepatic, CNS</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>R</td>
<td>60-200 min</td>
<td>300-400 mg/m²</td>
<td>800-2000 mg/m²</td>
<td>Hepatic, Renal</td>
<td>Hepatotoxicity, ototoxicity</td>
</tr>
<tr>
<td>Carmustine (BCNU)</td>
<td>H</td>
<td>30-45 min</td>
<td>100-200 mg/m²</td>
<td>300-600 mg/m²</td>
<td>Hepatic, lung CNS</td>
<td>Lung</td>
</tr>
<tr>
<td>Busulfan</td>
<td>H</td>
<td>1-7 hr</td>
<td>2-10 mg</td>
<td>16 mg/kg</td>
<td>Hepatic</td>
<td>Hepatic, Mucositis</td>
</tr>
<tr>
<td>Mephalan</td>
<td>Hydrolysis</td>
<td>45-60 min</td>
<td>30 mg/m²</td>
<td>140-200 mg/m²</td>
<td>Mucositis</td>
<td>Mucositis</td>
</tr>
</tbody>
</table>

Adapted from: BMT.2004;33: 259-269.
Busulfan (Bu)

- Alkylation agent
- Oral dosing: 1mg/kg PO q 6hrs
- Narrow therapeutic window
  - Too low of serum concentrations result in higher graft rejection and relapse rate
  - Too high of serum concentrations result in toxicities (hepatic veno-occlusive disease and seizures)
  - Many centers follow serum levels and individualize dosing
- Wide interpatient variability of pharmacokinetics with tradition oral formulation: 2mg tablets
  - Unpredictable intestinal absorption
  - Dosing uncertainties (Ex: emesis)
Intravenous busulfan (Busulfex)

- 60mg ampoules
- Significantly more expensive than oral
- FDA approved dosing: 0.8mg/kg IV q 6hrs
- Non-FDA approved dosing: 3.2mg/kg IV daily
- Comparative retrospective analysis of IV versus PO showed a significantly lower incidence in veno-occlusive disease and superior 100-day survival
Busulfan Toxicities

- **Seizures:** All patients should receive seizure prophylaxis (Phenytoin, Lorazepam, Clonazepam or newer agents).

- **Hepatic-veno occlusive disease (VOD):**
  - Life-threatening liver toxicity
  - Signs/symptoms (weight gain, increase in bilirubin, upper right quadrant pain/tenderness)
  - Prophylaxis: Low dose heparin, enoxaparin, or ursodiol are a few agents that some centers use.
  - Treatment: Usually involves defibrotide, an investigational agent available at some centers.
  - Many centers are using targeted busulfan dosing to obtain a specific range of exposure in an effort to reduce toxicities
Carboplatin (Carbo, Paraplatin)

- Traditionally, dosed based on AUC in solid tumor and lymphoma regimens to limit toxicities
- Targeted AUC dosing is less well documented in stem cell transplant regimens
- Utilized in a variety of solid tumor regimens
- Toxicities: Ototoxicity, hepatotoxicity, renal, cardiac
Carmustine (BiCNU, BCNU)

- Drug shortage over the past year and a half has been troublesome for transplant centers, currently available to transplant centers on a per patient basis. Some centers have had to abandon the use of BEAM for autologous transplants
- Alkylating agent
- Used in “BEAM” transplant preparative regimen (lymphomas): BiCNU+Etoposide, Cytarabine (Ara C), Melphalan
- Alkylating agent also used in treatment of brain tumors
- Adverse effects
  - Infusion related reactions
  - Pulmonary fibrosis
  - Hepatotoxicity
Cyclophosphamide (Cytoxan, Cy)

- Alkylating agent
- Bladder protectant, mesna, must be given
- Common dosing schedules
  - 120 mg/kg IV x 1 dose
  - 60 mg/kg IV daily x 2 doses
  - 2100 mg/m² x 2 doses
- Toxicities
  - Hemorrhagic cystitis (Mesna: bladder protectant)
  - Heart: Cardiac necrosis
  - Hepatic veno-occlusive disease (VOD)
Etoposide (VP-16, Toposar)

- Topoisomerase II inhibitor
- Utilized in a variety treatment regimens for AML, and NHL
- Utilized in BEAM preparative regimens, can be combined with TBI, cyclophosphamide, and carboplatin
- Usually administered either daily or twice a day and over a 2-4 days
- Toxicities
  - Mucositis
  - Secondary MDS/AML
Fludarabine (Fludara, Flu)

- Purine Analog
- Other similar agents: cladribine and pentostatin
- Utilized in treatment regimens for follicular lymphoma, CLL, AML, and ALL
- Usually administered over 3-5 days depending on the regimen
Fludarabine (Fludara, Flu)

- Toxicities
  - Thrombocytopenia
  - CNS
  - Peripheral sensorimotor neuropathy
  - Immunosuppression
Melphalan (Alkeran™)

- Alkylating agent
- FDA indication: For the palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate. >99% of use is “off-label”
- Mechanism of action: Bifunctional alkylation agent that is active against both resting and rapidly dividing tumor cells
- Dosing for transplant: 100-240mg/m²
Adverse effects: Melphalan

- Gastrointestinal: significant delayed nausea/vomiting, mucositis
- Hypersensitivity reaction
- Pulmonary: fibrosis, interstitial pneumonitis
Monoclonal antibodies

- Aletuzumab (Campath, anti-CD 52)
  - Used in the treatment of chronic lymphocytic leukemia (CLL)
  - T-cell depletion
- Rituximab (Rituxan, anti-CD20)
  - Used in the treatment of B-cell lymphomas
- Gemtuzumab (Mylotarg, anti-CD33)
  - Used in the treatment of acute myeloid leukemia
Monoclonal antibodies

- **Monoclonal antibodies are ideal for two reasons**
  - Highly active in a variety of diseases
  - Immunosuppressive, provides protection from GVHD
- **Toxicities**
  - Infusion related reactions
  - Opportunistic infections due to immunosuppression
Campath (Alemtuzumab)

- Monoclonal antibody targeting CD52
- CD52 is expressed on the surface of normal and malignant B and T lymphocytes, NK cells, monocytes, and macrophages
- FDA approved for the treatment of B-cell chronic lymphocytic leukemia in patients who have been treated with alkylating agents and have failed fludarabine therapy
The use of Campath in bone marrow transplant

- Appealing for the use in transplant due to its long half life (15-21 days) which translates to extensive T-cell suppression of the recipient. (Can last up to 6 months)

- Used in combination with reduced intensity regimens containing fludarabine and melphalan.
Advantages and disadvantages of using Campath immunosuppression in transplant regimens

- Given intravenously as part of the preparative regimen. (Less oral medication post transplant for the patient)
- Decrease incidence severe grade III/IV GVHD
- Cost (Campath is expensive)
- Increase risk for infectious complications

Blood.2002;99:1071-1078
Platinum derivative toxicities

- Cisplatinum
  - Nephrotoxicity
  - Neurotoxicity
  - Hypersensitivity
  - Ischemic vasculature events
- Carboplatin (see specific slides)
  - Myelosuppression
  - Nephrotoxicity
  - Neurotoxicity
  - Alopecia
- Oxaliplatin
  - Neurotoxicity
  - Pulmonary
  - Renal Toxicity
Thiotepa

- Alkylating agents
- Currently on drug shortage, unavailable to most transplant centers
- Used in variety of solid tumor preparative regimens and childhood caners
- Dose 360-1125 mg/m2
- Toxicities
  - Bone marrow suppression is the dose limiting adverse effect
  - Secondary AML or solid tumors
  - Mucositis
Agents use in the prevention of graft vs. host disease (GVHD)
Immunosuppression in Allogeneic Transplant Patients

- Immunosuppression focuses on
  - Inhibiting the activation of T-cells
  - Suppressing lymphocyte proliferation
  - Impairing antibody production
- Other mechanisms:
  - IL-2 receptor blockade
  - Inhibition IL-1, IL-7
  - Tumor necrosis factor blockade
Pharmaceuticals used in GVHD Prophylaxis

- Antilymphocyte globulins
- Antimetabolites
- Calcineurin-inhibitors
- Corticosteroids
- Monoclonal antibodies
- Mycophenolate
- Sirolimus
Examples of established pharmacologic immunosuppressive regimens for GVHD prevention

<table>
<thead>
<tr>
<th>Matched sibling</th>
<th>Mismatched sibling or unrelated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine (CSA)</td>
<td>CSA + Methotrexate (+1,+3,+6,(+11))</td>
</tr>
<tr>
<td>CSA + Methotrexate (+1,+3,+6)</td>
<td>CSA + Methotrexate + Steroids</td>
</tr>
<tr>
<td>CSA + Steroids</td>
<td>CSA + Anti-thymocyte/lymphocyte globulin</td>
</tr>
<tr>
<td></td>
<td>CSA + other Tcell depletion</td>
</tr>
</tbody>
</table>

Adapted from: *BMT.2000;25(2):S16-S19*
Other commonly used regimens

- Antilymphocyte globulins + cyclosporine
- Campath + cyclosporine
- Sirolimus + tacrolimus
- Antilymphocyte globulin + cyclosporine ± mycophenolate mofetil
- Incorporation of monoclonal antibodies
Antilymphocyte globulins (ATG)

- Because a portion of these agents contain either equine or rabbit, the human body recognizes it as foreign and severe drug reactions can result.
- Often requires pretreatment with corticosteroids, antihistamines and antipyretics.
Thymoglobulin (Anti-thymocyte globulin)

- Rabbit polyclonal anti T-cell antibody
- Another example of inhibiting T-cells
- FDA approved for use in renal transplant patients. However, utilized by many BMT centers as part of their preparative regimens
- Variety of dosing strategies employed
ATGAM

- Equine formulation
- First combined with prednisone and methotrexate
- Also utilized in treatment of acute GVHD
- Dosing varies among centers
Methotrexate

- Commonly used in stem cell transplant combination prophylaxis regimens
- Dosing: 5-15 mg/m² per dose
- Doses are usually given on days +1, +3, +7, +11 after transplant
- Used in combination with either cyclosporine or tacrolimus
- Side effects: worsening of mucositis (many centers are trying alternative prophylaxis to avoid methotrexate)
Calcineurin inhibitors

- Mechanism of action: Inhibit T-cells
- The hallmark of immunosuppression in both solid organ and stem cell transplant
- Products
  - Cyclosporine, cyclosporine-modified, (CSA, Neoral)
  - Tacrolimus, prograf, FK-506
Cyclosporine (CSA, Neoral)

- One of the oldest and most frequently used immunosuppressive agents
- Mechanism of action: calcineurin-inhibitor, inhibiting donor T-cell activation
- Different formulations: Sandimmune and Neoral (several generic cyclosporine-modified preparations are available).
Adverse effects of cyclosporine

- Hypertension
- Neurotoxicity
  - White matter changes (confusion)
  - Tremors
- Nephrotoxicity
  - Electrolyte wasting: potassium/magnesium
  - Increase in serum creatinine
- Drug interactions
  - Voriconazole
  - Calcium channel blockers, and some antibiotics to name a few
Tacrolimus = Prograf = FK-506

- Very similar mechanism of action as cyclosporine, calcineurin-inhibitor, thus cyclosporine and tacrolimus combination therapy in general is not acceptable
- Similar pathway of metabolism to cyclosporine: CYP450-3A4
- First used in solid organ transplant, first trials in stem cell transplant compared: tacrolimus + methotrexate to cyclosporine + methotrexate
Tacrolimus adverse effects

- Nephrotoxicity
- Neurotoxicity
- Hypertension
- Hyperglycemia
- Electrolytes: Magnesium wasting
- Drug interactions
  - Voriconazole
  - Fluconazole, Diltiazem, Oral contraceptives, Phenytoin, Antacids
Corticosteroids

- Methylprednisolone, prednisone most commonly used agents
- Agents are not optimal due to adverse effects
- Front-line treatment for ACUTE GVHD
- Adverse effects
  - Hyperglycemia
  - Stomacy ulcers
  - Psychosis
  - Increase risk of infection
  - Osteoporosis
Monoclonal antibodies

- Anti CD25 (Dacilzumab, Zenapax, AntiTAC)
- Alemtuzumab; Campath (see preparative regimen section)
- Rituximab (Rituxan)
- Infliximab (Remicade)
Daclizumab (Zenapx, CD52)

- Provides competitive inhibition of the binding of IL-2 to its receptor
- Majority of data: Steroid refractory treatment of acute GVHD
Rituximab

- Specific for CD20 found on B-cells
- Used in combination with chemotherapy as first-line treatment of nonhodgkin’s lymphoma
- Current ongoing studies evaluating utility in prevention of chronic GVHD
- Intermittent dosing after the first 100 days post transplant
Tumor necrosis factor blockade

- Infliximab
- Entercept
Infliximab (Remicade)

- Blocks the interaction between tumor necrosis factor and its receptors
- Indicated in a variety of autoimmune disorders
- Majority of data in transplant is in steroid refractory acute GVHD
Mycophenolate Mofetil = MMF = Cellcept

- Antimetabolite that selectively inhibits the proliferation of T and B lymphocytes by interfering with purine nucleotide synthesis
- MMF is a prodrug which is rapidly converted to its active form
- Available in oral and IV formulation
- Dosing is center specific: 1-2 grams/day in divided doses
- Studied in combination as a replacement to “mini” methotrexate
- Some centers are monitoring serum concentrations
Cellcept Adverse Effects/Toxicities

- In general, significantly less than other agents such as cyclosporine, tacrolimus
- Gastrointestinal: diarrhea, nausea
- Headache
- Hematologic (leukopenia, anemia, thrombocytopenia)
Sirolimus (Rapamune)

- Different mechanism of action than tacrolimus.
- Inhibits T-lymphocyte activation that occurs in response to antigenic and cytokine stimulation.
- Used in combination with tacrolimus in prevention of GVHD
- Also, has been incorporated into some centers treatment algorithms
Sirolimus: Adverse Effects

- Leukopenia
- Thrombocytopenia: seen within the first two weeks of therapy and improves thereafter
- Hypercholesterolemia
- Others: delayed wound healing, increase liver enzymes, hypertension, rash, acne, diarrhea and arthralgias
Sirolimus Pharmacokinetics and Toxicities

- Trough concentrations 5-15mg/dl
- Bioavailability ~ 30-45%: only available orally
- Metabolism via CYP4503A4
  - Many drug interactions
  - Voriconazole is a true contraindication
- Toxicities: generally less than cyclosporine and tacrolimus
  - Hypertriglyceridemia
  - Hypercholesteremia
  - Hematologic: thrombocytopenia, leukopenia
## Cost comparison of oral GVHD medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Frequency</th>
<th>Cost info</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine-modified (G)</td>
<td>150 mg</td>
<td>PO twice a day</td>
<td>$ 500-700/mon</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>1.5 mg</td>
<td>PO twice a day</td>
<td>$ 450-600/mon</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>500 mg</td>
<td>PO 3-4 x’s day</td>
<td>$500-700/mon</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>4 mg</td>
<td>PO daily</td>
<td>&gt; $ 600/mon</td>
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</tbody>
</table>
Mozobil (plerixafor, AMD3100)

- Approved Dec. 21st 2008
- Genzyme
- Mechanism of action: CXCR4 inhibitor which increases the amount of circulating stem cells that can be collected.
- Used for mobilization in autologous transplant
- Intended to be used with colony stimulating factor
Palifermin (Kepivance™)

- Human keratinocyte growth factor (KGF)
- KGF is an endogenous protein in the fibroblast growth factor family that binds to the KGF receptor.
- Binding of KGF to its receptor has been reported to result in proliferation, differentiation, and migration of epithelial cells.
Indications and Usage

- FDA approved 12/2004: Indicated to decrease the incidence and duration of severe oral mucositis in patients with hematologic malignancies receiving myelotoxic therapy requiring hematopoietic stem cell support.

- Safety and efficacy has not been established in patients with non-hematologic malignancies.
Precautions: Potential for stimulation of tumor growth

- The effects of palifermin on stimulation of KGF receptor-expressing, non-hematopoietic tumors in patients are not known.
- Palifermin has been shown to enhance the growth of human epithelial tumor cell lines in vitro and to increase the rate of tumor cell line growth in a human carcinoma xenograft model.
Adverse Effects: Palifermin

- ≥ 5% incidence in palifermin vs. placebo
  - Body as a whole
    - Edema, pain, fever
  - GI
    - Mouth/tongue Thickness or Discoloration
  - Musculoskeletal
    - Arthralgia
  - Skin
    - Rash, pruritus, erythema
  - Special senses
    - Altered taste
  - Metabolic
    - Elevated serum lipase/amylase
Palifermin dosing

- FDA: 60 mcg/kg/day IV bolus for 3 consecutive days before and 3 consecutive days after myelotoxic therapy for a total of 6 doses.
- Ongoing clinical trials evaluating “stacking doses” 180 mcg/kg/day prior therapy.
- **Approximate cost for course of therapy = $8,000**
- Now recommend in most recent MASCC/ISOO guidelines for TBI containing preparative regimens for autologous transplants.
Questions