HEMATOPOIETIC STEM CELL TRANSPLANTATION
CONDITIONING REGIMENS:
UNDERSTANDING THE COOKBOOK

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TIMELINE OF TRANSPLANT

Complications:
- Blood & Marrow Changes:
- Marrow failure
- Disease remission
- Disease recurrence

BMT Process:
- High-dose myeloablative therapy
- Primary diagnosis and treatment
- Relapse and salvage therapy

Supportive Therapy:
- Antibiotics
- Nutrition
- Antiemetics
- Growth factors
- Red cell transfusions
- Platelet transfusions
- Donor search or obtain autologous stem cells
- Chemo XRT
- PBSC/BM harvests in ABMT

Secondary tumors, cataracts, endocrine changes, QoL
- Acute and/or chronic GvHD
- Viral infections: CMV, VZV, PCP, IP
- Bacterial infections: HSV mucositis
- VOD

BM/SC re-infusion
- Marrow function
- Immune function

GOALS OF HSCT

- Provide stem cell replacement
  - Autologous and allogeneic
- Destroy malignancy
  - Conditioning (high-dose) therapy: auto and allo
  - Immunotherapy: allo (auto?)
WHAT IS THE DIFFERENCE BETWEEN AUTOTRANSPLANTS AND ALLOTRANSPLANTS?

<table>
<thead>
<tr>
<th>Autologous</th>
<th>Allogeneic</th>
</tr>
</thead>
<tbody>
<tr>
<td>support high dose chemo + XRT</td>
<td>replace immune system</td>
</tr>
<tr>
<td>risk of tumor contamination</td>
<td>no risk of tumor contamination</td>
</tr>
<tr>
<td>no immune effects</td>
<td>immune effects</td>
</tr>
<tr>
<td>lower treatment related deaths / morbidity</td>
<td>higher treatment related deaths / morbidity</td>
</tr>
</tbody>
</table>

DOSE RESPONSE AND CURABILITY OF HEMATOLOGICAL MALIGNANCIES

- Other Fatal Toxicity
- Bone Marrow Toxicity
- No Limiting Toxicity
- Relative Dose of Therapy Needed to Cure Tumor

SELECTION OF APPROPRIATE CONDITIONING REGIMEN

- Allogeneic or autologous transplant
- Disease and status of disease
- Prior therapy of disease and comorbidity
- T-depletion or graft manipulation
- Single or planned tandem SCT
- Experience of center
- Minimize regimen-related toxicity
FIRST QUESTION TO ANSWER:

- Based on it being something else
- Based on timing of agents
- Based on cellular support
- Because that is what your center uses

- Therapy prior to an autologous transplant is conditioning and is ablative

GVHD PROPHYLAXIS IS NOT CONDITIONING

- May begin before and continue after cells
  - Cyclosporine
  - Corticosteroids
  - Methotrexate (days +1, +3, +6, +11)
  - Mycophenolate (MMF)
  - Tacrolimus (FK56)
  - Sirolimus
  - ATG (maybe)

BASED ON TIMING

- If it is given AFTER the cells it is not conditioning
  - What about something given before and continued after?
CONFUSING THINGS

- ATG / ALG / Thymoglobulin
  - May be part of conditioning or considered GVHD prophylaxis
- Occasionally CYCLOPHOSPHAMIDE could be GVHD prophylaxis
  - When given after the cells

“ATG” EXAMPLES

- TLI + ATG
- FLU BU + THYMO (Days -2, -1, 0)
- BUCY + ATG (D+1 through +7)

WHY WAS THE THERAPY GIVEN?

- To facilitate engraftment (take) of the cells
  VS
- To debulk tumor
THE CELLS AND THEIR USE CAN HELP

All Hematopoietic Cells

CD34 +ve cells

True Stem Cells

Lymphocytes
TRYING TO ORGANIZE THE MADNESS

CONDITIONING AND THE THREE LITTLE BEARS

- Papa Bear: Traditional Ablative Regimens
- Mommy Bear: Reduced intensity regimens
- Baby Bear: Non-myeloablative regimens
- Red Riding Hood: CY + ATG for AA

CIBMTR “GROUPING”

- Working tool
- Best approximation
- Other drugs in addition need to be considered
- Important for clinical studies
- Round up
- Often no good answer
TRADITIONAL ABLATIVE

- Busulfan 16mg/kg po +
  cyclophosphamide (120 to 200
  mg/kg) +/- other
  - Also could have IV equivalent of
    busulfan
- Cyclophosphamide + TBI +/- other
  - Cyclophosphamide + VP16 + TBI

NON-TRADITIONAL
REDUCED INTENSITY CONDITIONING

- TBI
  - <500cGy in a single fraction
  - <800cGy fractionated
- LPAM (melphalan) <150mg/m2
- Busulfan <9mg/kg po or IV equiv
- BEAM, CBV
- VP16 + CY

EXAMPLES OF RIC
NON-MYELOABLATIVE REGIMENS: WORKING DEFINITION

• "A truly non-myeloablative regimen should allow relatively prompt hematopoietic recovery (<28 days) without a transplant, and mixed chimerism usually occurs upon engraftment following hematopoietic transplantation."
  Dick Champlin

NON-MYELOABLATIVE / VERY LOW INTENSITY

• Fludarabine + cyclophosphamide +/- rituximab (MDACC)

• Fludarabine + TBI 200cGy (Seattle)

SPECIFIC AGENTS: RATIONALE AND TOXICITIES
TBI - ADVANTAGES

- Rapidly delivered
- Immunosuppressive
- Short half-life (no metabolites)
- Not cross-resistant
- Good anti-leukemic
- Reaches privileged sites
- Can dose with targeting or shielding
- Does not require good blood supply

TBI - DISADVANTAGES

- Access to machine
- Toxic to normal tissues
  - Lung
  - Liver, Kidneys
  - Endocrine
  - Eyes
  - Second Cancers

RADIATION TOLERANCE OF NORMAL TISSUES
**BENEFITS OF ALKYLATOR THERAPY**

- Steep dose-response curve (dose escalation)
- Extramedullary toxicity is dose-limiting only at high dose
- Non-overlapping toxicity
- Capable of killing resting cells
- Not cross-resistant

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**BUSULFAN**

- Myeloablative
- Dosing by drug levels available
- Mucositis
- Veno-occlusive disease
- Pneumonitis
- Seizures

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**CYCLOPHOSPHAMIDE**

- Immunosuppression
- Not myeloablative
- Mucositis
- Hemorrhagic Cystitis
- Heart failure
# MELPHALAN

- Effective in hematologic malignancies
- Severe mucositis
- Late pneumonitis

# NON-HEMATOPOIETIC TOXICITIES OF CHEMOTHERAPEUTIC AGENTS USED IN HEMATOPOIETIC STEM CELL TRANSPLANTATION

<table>
<thead>
<tr>
<th>Agent</th>
<th>Heart</th>
<th>Lungs</th>
<th>Kidneys</th>
<th>Bladder</th>
<th>Mucosa</th>
<th>Liver</th>
<th>GI tract</th>
<th>Nervous system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Busulfan ++</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Carmustine (BCNU)</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>+++</td>
<td>+</td>
<td></td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Cytosine arabinoside</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Etoposide</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Thiopeta</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>

# COMMONLY USED HIGH-DOSE REGIMENS IN HEMATOPOIETIC STEM CELL TRANSPLANTATION

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dose-limiting toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide + TBI</td>
<td>Mucositis, VOD</td>
</tr>
<tr>
<td>Etoposide + TBI</td>
<td>Mucositis</td>
</tr>
<tr>
<td>Cyclophosphamide + cisplatin + carmustine (BCNU)</td>
<td>Pulmonary toxicity, VOD</td>
</tr>
<tr>
<td>Cyclophosphamide + carboplatin + thiopeta</td>
<td>Mucositis</td>
</tr>
<tr>
<td>Busulfan + cyclophosphamide</td>
<td>VOD, mucositis</td>
</tr>
<tr>
<td>Cyclophosphamide + etoposide + BCNU</td>
<td>VOD, mucositis</td>
</tr>
<tr>
<td>Ifosfamide + carboplatin + etoposide</td>
<td>Renal toxicity</td>
</tr>
</tbody>
</table>

TBI = total body irradiation; VOD = hepatic veno-occlusive disease
### MOST COMMONLY USED CONDITIONING AGENTS

<table>
<thead>
<tr>
<th></th>
<th>HLA-ident sib BMT-malignancy</th>
<th>Unrelated Donor BMT-malignancy</th>
<th>Auto-transplant Lymphoma</th>
<th>Auto-transplant Breast Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBI</td>
<td>52%</td>
<td>85%</td>
<td>25%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Cytoxan</td>
<td>87%</td>
<td>91%</td>
<td>85%</td>
<td>84%</td>
</tr>
<tr>
<td>Busulfan</td>
<td>48%</td>
<td>17%</td>
<td>10%</td>
<td>2%</td>
</tr>
<tr>
<td>Etoposide</td>
<td>24%</td>
<td>19%</td>
<td>73%</td>
<td>7%</td>
</tr>
<tr>
<td>Ara-C</td>
<td>5%</td>
<td>10%</td>
<td>25%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Thiotepa</td>
<td>4%</td>
<td>14%</td>
<td>8%</td>
<td>76%</td>
</tr>
<tr>
<td>Platinum*</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>7%</td>
<td>68%</td>
</tr>
<tr>
<td>Nitrosourea**</td>
<td>1%</td>
<td>&lt;1%</td>
<td>53%</td>
<td>10%</td>
</tr>
</tbody>
</table>

* cis-Platinum / carboplatin  ** BCNU / CCNU