Reporting Conditioning Regimen Intensity: ...ablative or not ablative, that is the question...

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Outline

- Rationale of different conditioning intensities.
- Classifications and operational definitions.
- Reporting conditioning intensity.

Hematopoietic Stem Cell Transplantation
- Classification -

- Allogeneic
  - HLA-identical
  - Other
- Syngeneic
- Autologous
- Donor
- Myneloablative
- Reduced Intensity
- Non-myneloablative
- Conditioning Regimen Intensity
- Bone marrow
- Peripheral Blood
- Umbilical cord blood
- Graft Source
- Ex vivo expansion
- In vivo selection
- Graft manipulation
**Goals of HSCT**

- Provide stem cell replacement
  - Autologous and allogeneic
- Destroy malignancy
  - High-dose chemotherapy/radiation
  - Immunotherapy
- Correct a genetic defect
  - Stem cells, immunodeficiency, inborn metabolic defects
- Disrupt an autoimmune disorder

**Conditioning Regimen**

- Conditioning or preparatory regimens are associated with morbidity and mortality after HCT.
- Transplantation candidates are carefully selected to optimize the success of this treatment.
- Important points for patient selection other than the primary disease and donor availability are:
  - Age
  - Comorbidities (performance status)

**Conditioning Regimen**

- Myeloablative effect
  - Toxicity to myeloid cells.
- Immune suppressive effect
  - Toxicity to lymphoid cells
- The conditioning regimen effect dependent upon:
  - Type of drug and combination
  - Radiation (location)
  - Overall dose
Timeline Of Transplant

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

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)

Dose Response And Curability Of Hematological Malignancies

Other Fatal Toxicity
Bone Marrow Toxicity
No Limiting Toxicity

Relative Dose of Therapy Needed to Cure Tumor

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>Cy + TBI</td>
<td>Mucositis, VOD</td>
</tr>
<tr>
<td>Etoposide (VP16) + TBI</td>
<td>Mucositis</td>
</tr>
<tr>
<td>Cy + cisplatin + Carmustine (BCNU)</td>
<td>Pulmonary toxicity, VOD</td>
</tr>
<tr>
<td>Cy + carboplatin + Thiotepa</td>
<td>Mucositis</td>
</tr>
<tr>
<td>Bu + Cy</td>
<td>VOD, mucositis</td>
</tr>
<tr>
<td>Cy + VP16 + BCNU</td>
<td>VOD, mucositis</td>
</tr>
<tr>
<td>Ifosamide + carboplatin + VP16</td>
<td>Renal toxicity</td>
</tr>
</tbody>
</table>
Conditioning Regimen Intensity

- **High Intensity**
  - Increase immediate anti-tumor effect
  - Increase toxicity
  - Relies on later graft versus disease effect
  - Decreased regimen related toxicity

- **Low Intensity**

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Reduced Intensity Regimens

- Expands the application of HCT to patients not previously considered candidates:
  - Older age
  - Comorbidities
  - Infections
- Not performed in patients with progressive disease.

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High and low regimen intensities, which one is better?

- Difficult to compare:
  - Population receiving reduced intensity regimens are generally sicker.
  - Transplant relate mortality appears lower
  - The rates of GVHD are the same.
### Selection Of Appropriate Conditioning Regimen

- 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

### Classification and Definitions

*Breathing pause...*

### Jargons

- **High Intensity**: ablative, myeloablative, traditional myeloablative
- **Low Intensity**: NST, nonmyeloablative, reduced intensity, minimally ablative
- **Other less desirable**: mini transplant.
### A Continuum of Conditioning Regimen Intensity

![Diagram showing A Continuum of Conditioning Regimen Intensity](image)

- **Immunosuppression**
  - Haplo / T-cell Dep
  - MUD
  - Matched sibling

- **GENETIC DISPARITY**
  - CLL / CML / LCL / AML
  - LGL / MM

- **AGGRESSIVENESS OF MALIGNANCY**
  - Cy + ATG + Thymic XRT
  - Haplo / T-cell Dep
  - MUD Matched sibling
  - Myelosuppression
  - z
  - TBI + Cy
  - TBI + F + TT
  - Bu16 + Cy
  - BEAM
  - FM
  - F + Cy
  - TBI 2Gy
  - Flag-Ida
  - FM

### Champlin Criteria for Non-myeloablative Regimens
- Prompt hematopoietic recovery (<28 days) without stem cell support.
- Mixed chimerism can be detected upon engraftment following hematopoietic transplantation.

### CIBMTR Working Definition
- Classifies according to specific doses.
- Best approximation, but not perfect.
- Other drugs or new regimen combination need to be considered
- Common criteria is important for clinical studies
Traditional Myeloablative

- TBI
  - ≥ 500cGy in a single fraction
  - ≥ 800cGy fractionated
- Busulfan ≥ 8mg/kg
  (or IV equivalent)
- Melphalan > 150 mg/m²
- Common Regimens: Bu/Cy and Cy/TBI

Reduced Intensity Conditioning

- TBI
  - <500cGy in a single fraction
  - <800cGy fractionated
- Busulfan < 8 mg/kg po or IV equiv
- Melphalan ≤ 150mg/m²
- Regimens:
  - BEAM (upper limit of RIC)
  - Etoposide/Cy
  - Bu/Flu
  - Flu/Mel/ATG

Nonmyeloablative

- TBI of 200cGy
- Regimens with purine analogs
  - Fludarabine, cladribine
- Others:
  - Flu/TBI (200cGy)
  - Flu/Cy
  - Flu/Ara-C/Idarubicin
  - Cladribine/Ara-C
EBMT Criteria of ReducedIntensity Conditioning

- TBI* (200-400 cGy)
- Busulfan* (8-10 mg/kg)
- Cyclophosphamide (600-1200mg/m²)
- Thiotepa (5-10 mg/kg)

* ± Fludarabine

Bredeson Three Little Bears Criteria

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

Food for Thought: It is not all about the dose

- Defining regimen intensity is complex.
- Considering drug or radiation doses only is suboptimal
- Important to consider individual differences
- Performance status and comorbidities matter
- The baseline disease also plays an important role (Fanconi Anemia)
Points to Consider

- Identify Conditioning regimen
  - Based on specific drugs
  - Based on timing of agents according to the stem cell infusion
- Familiarize with your center conditioning regimen preferences
- Therapy prior to an autologous transplant is conditioning and is ablative

BASED ON TIMING

- If it is given AFTER the cells it is not conditioning
  - What about something given before and continued after?
GVHD PROPHYLAXIS IS NOT CONDITIONING

- May begin before and continue after cells are infused:
  - Cyclosporine
  - Corticosteroids
  - Methotrexate
  - Mycophenolate (MMF)
  - Tacrolimus (FK56)
  - Sirolomus
  - ATG (maybe)
  - CAMPATH (maybe)

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)
### Specific Agents: Rationale And Toxicities

<table>
<thead>
<tr>
<th>Specific Agents</th>
<th>Rationale And Toxicities</th>
</tr>
</thead>
</table>

### TBI - Advantages

- Rapidly delivered
- Immunosuppressive
- Short half-life (no metabolites)
- Not cross-resistant
- Good anti-leukemic

### Radiation Tolerance Of Normal Tissues

<table>
<thead>
<tr>
<th>Organs</th>
<th>Tolerance Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow</td>
<td>600 R</td>
</tr>
<tr>
<td>Testis</td>
<td>1000 R</td>
</tr>
<tr>
<td>Lens</td>
<td>1500 R</td>
</tr>
<tr>
<td>Ovary</td>
<td>2000 R</td>
</tr>
<tr>
<td>Grow cartilage</td>
<td>3000 R</td>
</tr>
<tr>
<td>Kidney</td>
<td>4000 R</td>
</tr>
<tr>
<td>Lung</td>
<td>5000 R</td>
</tr>
<tr>
<td>Liver</td>
<td>7000 R</td>
</tr>
<tr>
<td>Heart</td>
<td>8000 R</td>
</tr>
<tr>
<td>Stomach &amp; intestine</td>
<td>9000 R</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>10,000 R</td>
</tr>
<tr>
<td>Brain</td>
<td></td>
</tr>
<tr>
<td>Salivary gland</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td></td>
</tr>
<tr>
<td>Urinary bladder</td>
<td></td>
</tr>
<tr>
<td>Mouth, pharynx &amp; esophagus</td>
<td></td>
</tr>
<tr>
<td>Bone (adult)</td>
<td></td>
</tr>
</tbody>
</table>
Benefits of Alkylation 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

Busulfan

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

Melphalan

- Effective in hematologic malignancies
- Severe mucositis
- Late pneumonitis
Cyclophosphamide

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

Pre-TED Conditioning Regimen Data Collection

- What was the intent of the regimen
  - My regimen is less intensive than yours...
- The reason for the choosing it:
  - Infectious, age, comorbidities
  - Prior HCT
- Collection of specific agents and regimens
- Future plans: collection of doses

Pre-TED
Pre-TED

Combine 2000 Recipient Baseline Data Form

191. Was pre-HSCT preparative regimen given?
1 ☐ yes
2 ☐ no

190. Specify protocol requirement: (check only one)
1 ☐ all agents given as outpatient
2 ☐ some, but not all, agents given as inpatient
3 ☐ all agents given as inpatient

191. Classify the recipient’s preparative regimen:
1 ☐ myeloablative
2 ☐ non-myeloablative (NST)
3 ☐ reduced intensity (RIC)

A Word on Chimerism
**Chimerism Analysis**

- Percent of donor and recipient
- Peripheral Blood or bone marrow
- Lineage specific or overall
  - Sorted (CD3/CD33)
- Dynamic during post transplant course
- Predicts disease relapse and secondary graft failure

**Conclusion**

- Identifying the specific regimen intensity is difficult and confusing
- The intent is important to know:
  - Know your center’s recipes.
- First tease out the conditioning from the GVHD prophylaxis.
- Other clues for reduced intensity:
  - Age and prior auto.
  - The comorbidities are not as simple
### 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>
</tr>
</thead>
<tbody>
<tr>
<td>TBI</td>
<td>52%</td>
<td>85%</td>
<td>25%</td>
</tr>
<tr>
<td>Cytoxan</td>
<td>87%</td>
<td>91%</td>
<td>85%</td>
</tr>
<tr>
<td>Busulfan</td>
<td>48%</td>
<td>17%</td>
<td>10%</td>
</tr>
<tr>
<td>Etoposide</td>
<td>24%</td>
<td>19%</td>
<td>73%</td>
</tr>
<tr>
<td>Ara-C</td>
<td>5%</td>
<td>10%</td>
<td>25%</td>
</tr>
<tr>
<td>Thiopeta</td>
<td>4%</td>
<td>14%</td>
<td>8%</td>
</tr>
<tr>
<td>Platinum*</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>7%</td>
</tr>
<tr>
<td>Nitrosourea**</td>
<td>1%</td>
<td>&lt;1%</td>
<td>53%</td>
</tr>
</tbody>
</table>

* cis-Platinum / carboplatin  ** BCNU / CCNU