CONDITIONING INTENSITY
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Disclosures

I have no relevant financial conflicts of interest to report.
Objectives

• Definition and classification of conditioning regimen and intensity
• Does the type of conditioning regimen matter?
• Types of regimens and different intensities
• Tips and overview of data collection (TED & CRF)
What is a Conditioning Regimen?

- Patients undergoing hematopoietic cell transplant (HCT) are prepared with a regimen of chemotherapy and/or radiotherapy, which is referred to as “conditioning”.
- Conditioning regimen has two objectives:
  - reduce the tumor burden—when the disease is cancer
  - suppress the recipient’s immune system, to allow engraftment of donor stem cells
Conditioning Regimens

- Vital component of transplantation procedure
- Many varieties of combination and intensities
- Data collection attempts to capture the exact intent, dose planned and given
- Updated classification on conditioning regimen types, incorporating current practices such as PK are needed.
Allogeneic Hematopoietic Cell Transplant: Factors that Impact Outcomes

- Conditioning Regimen
  - Anti-tumor
  - Immunosuppressive

- Graft source

- Donor

- Patient & Disease Characteristics

- Post-transplant supportive care
Indications for Allogeneic Transplants in Adults in the US, 2019

Donor type
- Related
- Unrelated

Frequency

Primary disease
Hematopoietic Cell Transplantation: Nomenclature

- **Allogeneic**
  - HLA-identical sibling
  - Other relative
  - Unrelated

- **Syngeneic**

- **Autologous**

- **Donor**

- **Graft Source**
  - Bone marrow
  - Peripheral Blood
  - Umbilical cord blood

- **Conditioning Regimen Intensity**
  - Myeloablative
  - Reduced intensity
  - Non-myeloablative

- **Outcomes**
  - TRM
  - Relapse
  - OS
  - RFS/LFS

Other important considerations:
Degree of HLA matching, CMV serology, patient and donor ABO compatibility, graft manipulation
Q1. Conditioning Regimen is an absolute requirement for allogeneic transplantation in adults.

- A. True
- B. False
Q1. Conditioning Regimen is an absolute requirement for allogeneic transplantation in adults.

- A. True* ✓
- B. False

*Exception: stem cell boost; however, the patient has received transplant already.
Conditioning Intensity

- Increased immediate anti-tumor effect
- Increased regimen-related toxicity
- Rely on later graft-versus-tumor effect
- Decreased regimen-related toxicity
CLASSIFICATION OF CONDITIONING REGIMENS FOR ANALYSIS PURPOSES

CIBMTR OPERATIONAL GUIDELINES
Operational Definition of CONDITIONING INTENSITY is based on the expected duration of pancytopenia and need for HSC support for hematopoietic recovery
Jargon

- High Intensity: (marrow) ablative, myeloablative
- Low Intensity: non-myeloablative, reduced intensity, minimally ablative
Reduced Toxicity Conditioning

- Newer Regimens with lower extra-medullary toxicity:
  - IV Busulfan/Flu, Flu/Treosulfan
- Allows for greater number of transplant-eligible patients
- Degree of toxicity is also dependent on the patient-related characteristics (end organ function, age, number of prior treatments)
Myeloablative (MA) Regimens:

1. TBI >5 Gy (single) or >8 Gy (fractionated)
2. CY +/- Etoposide (VP-16) + TBI (TBI >5 Gy [single] or TBI >8 Gy fractionated)
3. Busulfan (BU) >7.2 mg/kg IV (or >9.0 mg/kg PO) + CY
4. BU >300 mg/m^2 IV (or 375 mg/m^2 PO)
5. Mel >150 mg/m^2
6. Thiotepa (TT) >10 mg/kg
7. Treosulfan (Treo) >30,000 mg/m^2 (or >30 g/m^2)

1 Gray=100 centi-Gray (cGy)
Reduced Intensity Conditioning & Non-myeloablative Regimens

1. TBI \leq 5 \text{ Gy (single)} \text{ or } TBI \leq 8 \text{ Gy (fractionated)} +/- \text{ FLU}
2. CY +/- ATG +/- FLU
3. BEAM (BCNU + VP-16 + Ara-C + Mel)
4. BU \leq 7.2 \text{ mg/kg IV or } \leq 9.0 \text{ mg/kg PO}
5. BU \leq 300 \text{ mg/m}^2 \text{ IV or } \leq 375 \text{ mg/m}^2 \text{ PO}
6. Mel \leq 150 \text{ mg/m}^2 +/- \text{ FLU}
7. Treo \leq 30 \text{ g/m}^2 +/- \text{ FLU}
8. TT \leq 10 \text{ mg/kg}
Conditioning regimens fall on an intensity spectrum

Selection of Conditioning Regimen

• Younger patients (<55-65): MAC
  – BU-based are currently the most common
  – TBI >8 Gy – mainly in ALL

• Older patients and those with comorbidities- RIC/NMA

Does it matter what conditioning regimen/intensity is used?
Overall Survival of Recipients of IV-BU vs. TBI-based Myeloablative Conditioning

- IV- Bu: 56% (95% CI 53-60%) @ 2y
- TBI: 48% (95% CI 43-54%) @ 2y

P=0.019*

*pointwise p-value at 2 years

Allogeneic Transplant for AML: Randomized trial of two TBI regimens (12 Gy vs. 15.75 Gy)

Relapse and NRM are inversely related with increasing conditioning intensity

Clift RA et al. Blood. 1990; 76(9): 1867-1871
Comparing High doses of TBI in MAC: Registry study

Cumulative incidence of TRM by TBI dose

Cumulative incidence of relapse by TBI dose

Allogeneic Transplants and utilization by age (2000-2018)
Allogeneic Transplants in the US 2000-2018, by Conditioning Intensity and Age
Reducing the TRM: How much progress has been made?

TRM in matched sibling donor transplants

- 1985-1989 (n = 1,124)
- 1990-1994 (n = 1,283)
- 1995-1999 (n = 901)
- 2000-2004 (n = 460)

3-year P < .01

TRM in matched unrelated donor transplants

- 1990-1994 (n = 1,283)
- 1995-1999 (n = 901)
- 2000-2004 (n = 460)

3-year P < .01

EBMT study: Improved outcomes after allogeneic transplant using sibling donors

Caveats of Comparing Populations According to Conditioning Intensity in a Registry Study

![Diagram showing the comparison between MAC and RIC conditioning intensities based on various factors such as Age, Comorbidities, and Previous HCT. The diagram indicates eligibility criteria for both MAC and RIC.]
Myeloablative vs. reduced-intensity conditioning allogeneic transplant for CML

Patients

Patients with CML between 18 and 60 years of age who underwent allo-HCT using a sibling or unrelated donor between 2007 and 2014 were included in the study. Donors were matched to the recipients at the allele level at HLA-A, HLA-B, HLA-C, and HLA-DRB1 loci or mismatched at a single HLA locus. An upper age limit of 60 years was introduced as an inclusion criterion to restrict the patient population to a cohort where by age criteria both MAC and RIC would be feasible. Patients in the chronic phase (CP) or AP were included.

<table>
<thead>
<tr>
<th>Variable</th>
<th>MAC (n = 1204)</th>
<th>RIC (n = 191)</th>
<th>P</th>
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<td>60 (7-101)</td>
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<td>Number of centers</td>
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<td>Age at transplant, median (range), y</td>
<td>43 (19-60)</td>
<td>51 (19-60)</td>
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<tr>
<td>Age at transplant, y</td>
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<td>18-29</td>
<td>212 (18)</td>
<td>17 (9)</td>
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<td>30-39</td>
<td>276 (23)</td>
<td>21 (11)</td>
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<td>404 (34)</td>
<td>47 (25)</td>
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<td>525 (44)</td>
<td>64 (34)</td>
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<td>132 (11)</td>
<td>27 (14)</td>
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<td>3+</td>
<td>248 (20)</td>
<td>58 (30)</td>
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MAC vs. RIC in AML and MDS (BMT CTN 0901)

Scott BL, et al. JCO 35: 1154-1161
BUCY vs. FluBU: Phase III randomized trial in AML patients (40-65 years)

TRM ↑ with BuCy

LFS ↑ with FluBU

Reduced Toxicity Myeloablative vs. Reduced Intensity Conditioning: FluTreo vs. FluBU

Relapse ↔ HR 0.87 (95% CI 0.59-1.30); p=0.50

TRM ↑ with FluBU HR 0.54 (95% CI 0.32-0.9); p=0.02

OS ↑ with FluTreo HR 0.61 (95% CI 0.42-0.88); p=0.0082

Anti-Thymocyte Globulin (ATG)

- Is it conditioning or GVHD prophylaxis?
- ATG is considered *in vivo* T-cell depletion
- Tip:
  - **Report as conditioning**: if the intent is to allow engraftment, usually given at lower dose at the start of the conditioning.
  - **Report as GVHD prophylaxis**: if the intent is such, usually given at high doses close to stem cell infusion.
Spectrum of Intensity of commonly used Conditioning Regimens

Intensity of the Conditioning Regimen

Non-myeloablative
- Flu TBI (2 Gy)
- Flu Cy TBI (2 Gy)
- TBI (2 Gy)
- TLI - ATG

Reduced Intensity Conditioning
- Flu BU2 (BU 6.4 mg/kg IV)
- Flu Mel
- Flu Mel TT (<10 mg/kg)
- Flu Treo (30 g/m²)
- BEAM

Myeloablative
- BU CY
- CY TBI (12 Gy)
- TBI (12 Gy) VP-16

Reduced Toxicity Myeloablative Conditioning
- Flu BU4 (12.8 mg/kg IV)
- Flu BU3 (9.6 mg/kg IV)
- Flu Treo 36-42 g/m²
How do I determine the intensity of conditioning regimen?

**Yes**

Single fraction: >5 Gy = MAC; Single fraction ≤5 Gy = RIC; if CY+TBI = MAC

**No**

Alkylating agent in conditioning regimen

**Yes**

If CY with BU = MAC; all others = RIC

**No**

No TBI + no alkylating agent = RIC

**MAC** = Myeloablative Conditioning

**RIC** = Reduced Intensity Conditioning

**RT-MAC** = Reduced Toxicity Myeloablative Conditioning
Q2. Which regimen is myeloablative?

1. Fludarabine 120 mg/kg IV + Busulfan 6.4 mg/kg IV
2. Busulfan 12.8 mg/kg IV + Cyclophosphamide 120 mg/kg IV
3. Fludarabine 120 mg/kg IV + TBI 2 Gy (single fraction)
4. BEAM (Carmustine 300 m/m² IV + Etoposide 800 mg/m² IV + Cytarabine 800 mg/m² IV + Melphalan 140 mg/m² IV)
5. Fludarabine 150 mg/m² + Busulfan 12 mg/kg PO
Q2. Which regimen is myeloablative?

1. Fludarabine 120 mg/kg IV + Busulfan 6.4 mg/kg IV
2. Busulfan 12.8 mg/kg IV + Cyclophosphamide 120 mg/kg IV √
3. Fludarabine 120 mg/kg IV + TBI 2 Gy
4. BEAM (Carmustine 300 m/m² IV + Etoposide 800 mg/m² IV + Cytarabine 800 mg/m² IV + Melphalan 140 mg/m² IV)
5. Fludarabine 150 mg/m² + Busulfan 12 mg/kg PO √
Q3. Which regimen is reduced intensity?

1. Fludarabine 120 mg/kg IV + Busulfan 6.4 mg/kg IV
2. Busulfan 12.8 mg/kg IV + Cyclophosphamide 120 mg/kg IV
3. Fludarabine 120 mg/kg IV + Melphalan 140 mg/m² IV
4. Cyclophosphamide 120 mg/kg IV + TBI 12 Gy in 6 fractions
5. Fludarabine 150 mg/m² + Busulfan 16 mg/kg PO
Q3. Which regimen is reduced intensity?

1. Fludarabine 120 mg/kg IV + Busulfan 6.4 mg/kg IV √
2. Busulfan 12.8 mg/kg IV + Cyclophosphamide 120 mg/kg IV
3. Fludarabine 120 mg/kg IV + Melphalan 140 mg/m² IV √
4. Cyclophosphamide 120 mg/kg IV + TBI 12 Gy
5. Fludarabine 150 mg/m² + Busulfan 16 mg/kg PO
Collection of Conditioning Data

- Weight (Actual/Dosing)
- Was a preparative regimen given
- Classification of regimen intensity (Intent)
- Date of regimen
- Irradiation/Total Fractions
- Drugs, Mode, Doses
- Pharmacokinetics (CRF only)
Collection of Conditioning Regimen Information: TED vs. CRF

**Total Dose**
- CRID Form 2804

**Weight**
- CRID Form 2804

**Pre-TED**
- Prescribed: 2400 mg/kg, 2804 mg/m²
- Targeted AUC

**Baseline Form**
- Given: 2000 mg
- Dosing Weight

**HCT**
- 60d
- 100d
Calculation of Dosing Body Weight (DBW)

DBW = IBW* + 0.4 (ABW^-IBW)
DBW = 150 lbs + 0.4 (250-150)
DBW = 150 lbs + 40 lbs
DBW = 190 lbs (or 86.4 kg)

*IBW = Ideal Body Weight
^ABW = Actual body weight

Other terms used for DBW:
• AIBW (adjusted ideal body weight),
• AjBW (adjusted body weight),
• CIBW (corrected ideal body weight)
Patient Scenario #1

Jane’s prep regimen consists of:

- Busulfan 130 mg/m² daily x 4 doses
- Fludarabine 40 mg/m² daily x 4 doses

Height = 62 inches
ABW = 65 kg
DBW = 54 kg
BSA = 1.53 m²
Determining Chemotherapy Dose

How is the BU dose calculated?
130 mg/m² x 4 doses = 520 mg/m²
520 mg/m² x 1.53 m² = 796 mg
(or 800 mg)

How is the FLU dose calculated?
40 mg/m² x 4 doses = 160 mg/m²
160 mg/m² x 1.53 m² = 245 mg
(or 240 mg)
Chemotherapy Reporting
Form 2400

• The total prescribed dose to report on F2400 for BU should be 520 mg/m$^2$ & for FLU 160 mg/m$^2$

• However, this is what was reported for Jane…
Chemotherapy Reporting

- On **F2400**, the following was reported-
  Bu 130 mg/m²
  Flu 40 mg/m²

- On **F2000**, the following was reported-
  Bu 800 mg
  Flu 240 mg
Chemotherapy Reporting

If BU 130 mg/m² was the total prescribed dose, then the total dose reported on Form 2000 for BU should have been **200 mg** instead of **800 mg** based on Jane’s BSA.
Pre-TED dose reporting affects Baseline reporting

If the correct total prescribed BU dose of 520 mg/m² had been reported on the Pre-TED, then 800 mg reported on the Baseline form would be correct.
Patient Scenario #2

A 65-year-old female with IgG kappa myeloma is being admitted for an autologous HCT. The written chemotherapy orders state Melphalan 70 mg/m² IV daily x 2 days.

- The height of the patient is 159 cm
- Actual body weight (ABW) = 72 kg
- Dosing body weight (DBW) = 59 kg
- BSA = 1.6 m²
Q4. What is the total prescribed *Melphalan* dose to report on Form 2400 Q129 for the preparative regimen?

A) 70 mg/kg  
B) 70 mg/m²  
C) 140 mg/kg  
D) 140 mg/m²
Q4. What is the total prescribed cumulative *Melphalan* dose to report on Form 2400 Q129 for the preparative regimen?

A) 70 mg/kg
B) 70 mg/m²
C) 140 mg/kg
D) 140 mg/m²  √
Chemotherapy Reporting Form 2000

• The actual *Melphalan* dose the patient received would be found in the chemotherapy administration records (MAR).

• **Form 2000** – The dose would have been calculated using the patient’s BSA.
Chemotherapy Reporting
Form 2000

70 mg/m² x 1.6 m² = 112 mg daily

Daily dose x BSA

What is the total dose given?

112 mg x 2 days = 224 mg

Total Melphalan dose given
Chemotherapy Reporting
Form 2000 - Patient Scenario # 2

Q5. What is the total Melphalan dose actually given that would be reported on Form 2000 Q78?

A) 70 mg
B) 112 mg
C) 140 mg
D) 224 mg
Chemotherapy Reporting
Form 2000 - Patient Scenario # 2

Q5. What is the total *Melphalan* dose actually given that would be reported on Form 2000 Q78?

A) 70 mg
B) 112 mg
C) 140 mg
D) 224 mg √
Questions