Why, When and Where to Report Conditioning Regimens
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Objectives

• Rationale of conditioning or preparative regimen
• Does the type of conditioning regimen matter?
• Types of regimens and different intensities
• Tips and overview of data collection (TED & CRF)
Q#1 What are conditioning regimens

A. A combination of different hair styling products
B. Chemotherapy or irradiation prior to transplant used to allow engraftment of donor cells and/or control a malignant disease
C. Behavioral modification approaches
D. A new diet
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Allogeneic Hematopoietic Stem Cell Transplantation

**Conditioning Regimen**
- Anticancer
- Myeloablative
- Immunosuppressive

**Hematopoietic stem cells**

**Post-transplant supportive care**

**Graft sources**
- Bone
- Peripheral Blood
- Umbilical cord blood

**Allogeneic**
- HLA-identical
- Other relative
- Unrelated sibling
Hematopoietic Stem Cell Transplantation
- Classification -

Other important considerations:
• Degree of HLA matching
• CMV serology, patient and donor
• ABO compatibility
• Graft manipulation
Graft vs Host Disease/Graft Rejection

HLA differences stimulate detrimental immune responses

Patient → GvHD → Rejection → Donor Stem Cells
Q#2 Conditioning Regimen is an absolute requirement for transplantation.

- A. True
- B. False
Q#2 Conditioning Regimen is an absolute requirement for transplantation.

• A. True*
• B. False

*Exception is in case of stem cell boost….however the patient has received a transplant already.
Collection of Conditioning Data

• Weight
• Was a preparative regimen given
• Classification of regimen intensity
• Date of regimen
• Irradiation/Total Doses
• Drugs
• Pharmacokinetics (CRF only)
Calculation of Dosing Body Weight (DBW)

\[
DBW = IBW + 0.4(ABW-IBW)
\]

\[
DBW = 150 \text{ lbs} + 0.4(250-150)
\]

\[
DBW = 150 \text{ lbs} + 40 \text{ lbs}
\]

\[
DBW = 190 \text{ lbs} \text{ (or 86.4 kg)}
\]

IBW = Ideal Body Weight
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
Determining Chemotherapy Dose

How is the Busulfan 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 Fludarabine dose calculated?
40 mg/m² x 4 doses = 160 mg/m²
160 mg/m² x 1.53 m² = 245 mg
(or 240 mg)
• The total prescribed dose to report on F2400 for Busulfan should be 520 mg/m² & for Fludarabine 160 mg/m²

• 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 the patient’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 is correct.
Conditioning Regimen Intensity

- Increase immediate anti-tumor effect
- Increase toxicity

- Rely on later graft versus disease effect
- Decreased regimen related toxicity

Number of candidates for HCT
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.
A Continuum of Conditioning Regimen Intensity

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

**Myelosuppression**
- TBI 2Gy
- Flag-Ida
- BEAM
- FluMel
- Bu8+F+ATG
- Flu/Bu4
- Bu16+Cy
- TBI+Cy
- TBI+F+TT

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

**AGGRESSIVENESS OF MALIGNANCY**

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CLASSIFICATION OF PREPARATIVE REGIMENS FOR ANALYSIS PURPOSES

CIBMTR OPERATIONAL GUIDELINES
Jargons

- **High Intensity**: ablative, myeloablative, traditional myeloablative
- **Low Intensity**: NST, nonmyeloablative, reduced intensity, minimally ablative
- Other less desirable: mini, transplant lite.
- Papa bear, mama bear and baby bear....
Myeloablative (MA) Regimens:

1) TBI >500 cGy (single) or >800 cGy (fractionated)

2) Cyclophosphamide (Cy) + TBI (TBI >500 cGy (single) or TBI >800 cGy fractionated)

3) Cy + VP16 + TBI (TBI >500 cGy (single) or TBI >800 cGy fractionated)
MA Regimens (continued)

4) Busulfan (Bu) >7.2 mg/kg **IV** (or >9.0 mg/kg **po**)

5) Bu >300 mg/m2 **IV** (or 375 mg/m2 **po**)

6) Bu >7.2 mg/kg **IV** (or >9.0 mg/kg **po**) + Cy

7) Bu >7.2 mg/kg **IV** (or >9.0 mg/kg **po**) + Melphalan >150 mg/m2
MA Regimens (continued)

8) Melphalan > 150 mg/m²
9) Thiotepa > 10 mg/kg
10) Treosulfan > 30,000 mg/m² (or > 30 g/m²)
11) Addition of clofarabine
Reduced Intensity Conditioning & Non-myeloablative Regimens

1) TBI $\leq 500$ cGy (single) or TBI $\leq 800$ cGy (fractionated)
2) ATG + Cy
3) BEAM
4) Bu $\leq 7.2$ mg/kg IV or $\leq 9.0$ mg/kg po
5) Bu $\leq 300$ mg/m$^2$ IV or $\leq 375$ mg/m$^2$ po
6) Melphalan $\leq 150$ mg/m$^2$
RIC/NMA Regimens (continued)

7) Fludarabine + ARA-C
8) Fludarabine + Cy
9) Fludarabine + TBI (TBI ≤500 cGy (single) or TBI ≤800 cGy (fractionated)
10) Thiotepa ≤10 mg/kg
11) Treosulfan ≤30,000 mg/m2 (or ≤30 g/m2)
12) VP16 + Cy
Regimen Definitions and Abbreviations

Operationally Defined

Basis: expected duration of cytopenia & need for HSC support for recovery

MA: irreversible cytopenia & mandatory HSC support

NMA: minimal cytopenia & do not need HSC support

RIC: a regimen that does not fulfill MA or NMA criteria

Bacigalupo et al; BBMT 2009; 15: 1628
Myeloablative Conditioning Regimen

- Younger patients
- Busulfan based are the currently most commonly done in the country
- TBI >800cGY – mainly in ALL
- Does it matter?
Overall Survival of Recipients of IV-BU Compared to TBI-based Myeloablative Conditioning for Malignant Diseases

IV- Bu: 56% (95% CI 53-60%) @ 2y

TBI: 48% (95%CI 43-54%) @2y

P=0.019*

*pointwise p-value at 2 years

Bredeson C et al, Blood 2013
How about timing of transplant?

• The order of how drugs are given may alter its side effect profile....
Transplant Outcomes by Cy and TBI Sequence

Treatment-related Mortality

Progression/Relapse

Progression-free Survival

Overall Survival

Holter-Chakrabarty J et al Tandem 2014
Conditioning Regimens: Paradigm Change

OLD

• Engraftment requires marrow ablation

• Conditioning regimen is the mainstay for tumor eradication

• Linear dose-response relationship between cytotoxicity and tumor kill

• Narrow Therapeutic window

NEW

• Host immune suppression & survival advantage for donor HSC are key

• Graft versus Tumor Effect is significant in many diseases

• Traditional conditioning --- prohibitive toxicity in older patients & those with comorbidities

• Wider Therapeutic Index with lower intensity conditioning
Conceptual development reduced intensity transplants - with T cell replete grafts -

Recipient

Donor

T-replete SCT

200 cGy TBI

MMF/CSP

Mixed Donor/Host Chimerism

GVHD

Correction of Immune Deficiency, Genetic, Autoimmune Diseases

Full Donor Chimerism

Cure of Malignant Diseases

Low intensity conditioning

Acknowledgment to R. Storb
TRANSPLANT-RELATED MORTALITY BY AGE
Standard vs. Reduced Intensity Conditioning

Myeloablative
Reduced Intensity

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NRM and REL cumulative incidence estimates (36-month) from a competing risk model, estimated separately for both conditioning regimens for MDS

- Standard:
  - NRM = 32%
  - REL = 27%

- RIC:
  - NRM = 22%
  - REL = 45%
Leukemia-free survival of patients 40+ years receiving RIC allogeneic HSCT for AML in CR1, 1995-2005, by age

$p=0.71$

Luger S. et al Blood 2010
Overall Survival after HCT for Acute Leukemia with RIC vs. Myeloablative conditioning regimens

Leukemia (2005) 19, 2304–2312
Caveats of Comparing Populations According to Regimen Intensity

- **Myeloablative**
  - +/- no Comorbidities
  - Previous HCT

- **RIC**
  - +++ yes Age

Eligibility
Within low intensity regimens

• Not all regimens are created equal
• Concepts
  – Disease specific vs. general immunoablative regimens (FCR vs. low dose TBI in lymphoma)
• Difficult to discern regimen from regimen/GVHD prophylaxis packages
Comparison of TBI vs. non TBI-based nonmyeloablative conditioning regimens for lymphoma

Hong S. et al, BBMT 2014
Reduced Toxicity Concept

- Newer Regimens with lower extra-medullary toxicity:
  - IV Busulfan/Fludarabine, treosulfan
- Allows for extending the number of eligible patients.
- The degree of toxicity is also dependent on the patient-related characteristics (end organ function, age, number of prior treatments)
How about ATG?

• Is it part of the 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.
Autologous HCT Conditioning Regimen

• High dose therapy with stem cell rescue
  – This is true for malignant diseases
  – Intent is to escalate the intensity to maximize disease control

• Does the concept of reduced intensity exist in autologous HCT?

Yes, mainly in autoimmune diseases, where immunoablation is the main focus.
Comparison of Conditioning Regimens prior to AutoHCT for Follicular Lymphoma

Chen Y. et al BBMT 2015
Comparison of Conditioning Regimens prior to AutoHCT for Diffuse Large Cell Lymphoma

Chen Y. et al BBMT 2015
Comparison of Conditioning Regimens prior to AutoHCT for Mantle Cell Lymphoma

Chen Y. et al BBMT 2015
Comparison of Conditioning Regimens prior to AutoHCT for Hodgkin Disease

Chen Y. et al BBMT 2015
Shorter PFS among patients with HL after BuCyE conditioning compared with BEAM

Pasquini MC et al, BMT Tandem 2014
Patient Scenario #2

A 65 yo female with IgG kappa myeloma is being admitted for an autologous HCT. The written chemotherapy orders state Melphalan 70 mg/m$^2$ 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 m$^2$
Chemotherapy Reporting
Form 2400

What is the total prescribed cumulative Melphalan dose to report on Form 2400 Q252 for the preparative regimen?

A) 70 mg/kg
B) 70 mg/m$^2$
C) 140 mg/kg
D) 140 mg/m$^2$
Chemotherapy Reporting Form 2000

- The actual Melphalan dose the patient received would be found in the chemotherapy administration records.
- 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

What is the total Melphalan dose **actually** given that would be reported on Form 2000 Q192?

A) 70 mg  
B) 112 mg  
C) 140 mg  
D) 224 mg
Conditioning Regimens

- Vital component of HCT
- 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.
Questions
ESTIMATED NUMBERS OF POTENTIAL TRANSPLANT CANDIDATES vs. TRANSPLANT RECIPIENTS IN U.S.

- NHL: 55,000
- MM: 15,000
- AML: 11,000
- HD: 8,000
- CLL: 7,500
- CML: 4,500
- ALL: 4,000

NUMBERS IN THOUSANDS

- Allografts
- Autografts

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