Rational Combination of Cytotoxic Agents in Personalized Therapy of Malignant and non-Malignant Diseases

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April 28, 2017

Molecular Pharmacology and Translational Drug Development Program
...limited to Stem Cell Transplantation
WHY think rationally?

(Based on Reason)
Conditioning = Immunosuppression ??

1. Conditioning

2. Patient (age, gender, CMV, comorbidities...)

3. Disease features

4. Graft

5. Supportive Care

6. GVHD prophylaxis / therapy

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Figure 1

Cumulative incidence of graft failure by cyclophosphamide dose Number at risk

Overall survival (actuarial estimate) for the whole group (n=20) (curve A) and for the thirteen patients treated according to Bacigalupo et al.\textsuperscript{1} (curve B). SCT: stem cell transplant.
Allo-SCT in Thalassemia, Only Alternat. Donor Study till 2016

31 HAPLOIDENTICAL TRANSPLANT IN THALASSEMIA

- Survival: 93%
- Thalassemia-Free Survival: 70%
- Rejection: 23%
- Non-Rejection Mortality: 7%

2 died, 7 rejected

Sodani and Lucarelli, Ped Repts 2011;3:e13

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CONDITIONING/IMMUNOSUPPRESSION

UNDERSTANDING THE DRUGS USED FOR IMMUNOSUPPRESSIVE AND CYTOTOXIC EFFECTS
GOING BACK TO THE BASICS OF BETTER UNDERSTANDING THE FUTURE

- CYTOTOXICITY: What is That?
- IMMUNOSUPPRESSION: What is That?
Regarding Conditioning

- **CYTOTOXICITY:**
  a. Kill the malignant cells.
  b. Kill the immunocompetent cells responsible for graft rejection.

- **IMMUNOSUPPRESSION:**
  a. Get engrafted, stay engrafted.
Regarding Conditioning

- CYTOTOXICITY:
  a. Kill the malignant cells.
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- IMMUNOSUPPRESSION:
  a. Get engrafted, stay engrafted.
IS DRUG SEQUENCING AND TIMING IMPORTANT FOR CYTOTOXICITY?

[applied to NAs and Busulfan (AA)]
Sequence and Timing of Fludarabine and Busulfan

Drug 1
0 hrs

Drug 2
8 hrs

Drug 2
24 hrs

MTT
24 hrs

MTT
24 hrs

Valdez B, and Andersson, BS. Unpubl.

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Sequence and Timing of Fludarabine and Busulfan

Valdez B, and Andersson, BS. Unpubl.

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The Loop of Death

- DNA synthesis/repair
- DNA damage
- DNA cross-linking
- Chromatin remodeling
- DNA alkylation agents (AAs)
- Histone deacetylase inhibitors (HDACi)
- Histone modifications
- Hypomethylating agents
- Nucleoside analogues (NAs)

Apoptosis

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Valdez B, and Andersson, BS. Environ Mol Mutagen 2010;51:659-68
SEQUENCE AND TIMING ARE IMPORTANT FOR THE RESULTING CYTOTOXICITY

[applied to NAs and Busulfan (AA)]

Really, Clinically?
# Flu - IV Bu Reduced-Tox Conditioning

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**PK** d. 1 and d. 3 or 4
*day of ATG if MUD or 1-Ag mm.

**BM/PBPC day 7**
Survival - patients in CR at transplant

Time in months

Proportion Surviving

BuFlu

BuCy2

P=0.01

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Andersson BS et al. BBMT 2008;14:672-79
Figure 1 Cumulative incidence of relapse (A), transplant related mortality (TRM) (B), overall survival (OS) (C) and disease free survival (DFS) (D). The 5-year cumulative incidence of relapse were 16.5 ± 5.8% and 16.2 ± 5.3% in BuCy and BuFlu group (P = 0.943). The 5-year cumulative incidence of TRM were 18.8 ± 6.9% and 9.9 ± 6.3% in BuCy and BuFlu group (P = 0.104). The 5-year cumulative OS were 72.3 ± 7.9% and 81.9 ± 7.0%, respectively, in BuCy and BuFlu group (P = 0.177), and DFS were 67.4 ± 7.6% and 75.3 ± 7.2%, respectively, in BuCy and BuFlu group (P = 0.215).
BuCy2 vs Bu-Flu in AML

Figure 3: Kaplan-Meier curves of leukaemia-free survival (A) and overall survival (B)

**Flu - IV Bu Reduced-Tox Conditioning**

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G** = BM/PBPC day 8
BuCy2 vs Bu-Flu in Advanced Hematological Malignancies

**Figure 2.** Survival differences between the busulfan-cyclophosphamide (BuCy) and busulfan-fludarabine (BuFlu) arms. (A) Overall survival; (B) relapse-free survival; (C) nonrelapse mortality; (D) event-free survival. HCT, hematopoietic cell transplantation.

JCO, Lee et al. JCO 2013;31:701-09
SEQUENCE AND TIMING ARE CRUCIALLY IMPORTANT FOR THE RESULTING CYTOTOXICITY

[applied to NAs and Busulfan (AA)]
IS DRUG DOSE IMPORTANT FOR CYTOTOXICITY?

BTW: Dose?

Dose Administered, or the resulting Systemic Drug Exposure?
Pharmacokinetic Targeting of a Therapeutic Window

Risk of Leukemia Progression and Graft Failure

Systemic Drug Exposure

Fraction, Patients at Risk

Fraction, events

PK-Guided

Fixed-Dose

Safe Limit, Syst. Exposure

Normal Organ Toxicity

"EXCESSIVE TOXICITY"

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Fludarabine-Busulfan
Randomized study of busulfan dosing

AML/MDS

- PK-Adjusted dose AUC 6000 µMol-min
- Fixed dose 130 mg/m², resulting in an average AUC ~5000 µMol-min

The PK-adjusted Dose group will have an average dose escalation of ~20% and a consistent AUC at that level.

Andersson BS et al BMT. 2017;52:580-87
OS and PFS is Better after PK-guided Bu dosing in AML/MDS

Figure 1a. Overall Survival – All Patients
(Fixed Dose N=107, number of deaths=65;
PK-Guided Dose N=111, number of deaths=50)

Figure 1b. Progression-Free Survival – All Patients
(Fixed Dose N=107, number of events=67;
PK-Guided Dose N=111, number of events=55)

Andersson BS et al BMT. 2017;52:580-87

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Progression-Free Survival, Non-CR Patients

Andersson BS et al BMT. 2017;52:580-87

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Posterior Probability = 0.922 that PK-Guided is Superior to Fixed Dose IV Busulfan

Andersson BS et al BMT. 2017;52:580-587
Optimized (Conditioning)-Therapy Improves outcome!!

1. Conditioning

2. Patient (age, gender, CMV, comorbidities...)

3. Disease features

4. Graft

5. Supportive Care

6. GVHD prophylaxis / therapy

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Regarding Conditioning-Immunosuppression

- IMMUNOSUPPRESSION: Get engrafted, stay engrafted.

- CYTOTOXICITY:
  a. Kill the malignant cells.
  b. Kill the immunocompetent cells responsible for graft rejection.

(What is “kill the – cells” ?)
Categories:

1. Slow apoptosis/induced senescence
e.g. busulfan, nucleoside analogs

2. Radiomimetic; mixture of slow / rapid apoptosis
e.g. Thiotepa, melphalan, cyclophosphamide

3. Interphase cell death/necrosis; XRT

e.g. ATG, Campath.
Optimizing the Conditioning Therapy

Hypothesis: The Conditioning Therapy delivers immunosuppression that can be considered to consist of 3 parts:

1. Killing host mature cytotoxic T-cells,  
   \[ +++ - +/- \]

2. Removing T-cells, other Immunoreactive cells  
   \[ +++ - +/- \]  
   (Cf. necrosis/mitotic catastrophe/rapid apoptosis/ATG).

3. Killing host (Immunoreactive) stem cells  
   \[+++++\]

Enigma: In many Genetic Diseases the Immune System is active or hyperactive, no previous chemotherapy history.

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Now,

Let’s consider Genetic Disorders
After all, they are among the most difficult to treat:

1. Children
2. Not cancer
3. Kill (Often) slowly, difficult Benefit-Risk calculation
“Immuno-ablative Therapeutic Intervals”

- Thalassemia-SCA Patients - Immunocompetent
- Leukemia Patients - Immunosuppressed
- SCID

- Systemic Drug Exposure
- "Safe Upper Limit", Syst. Exposure
- aGVHD
- Normal Organ Toxicity

Fraction of Non-Engrafted Patients vs. Systemic Drug Exposure
“Immuno-ablative Therapeutic Intervals”

Hemoglobinopathies/ e.g. Thalassemia, SCA Immunocomp. Pats.

Systemic Drug Exposure

Fraction of Patients

2;BuCy2 1;BuCy4

"Safe Upper Limit", Syst. Exposure

aGVHD

Normal Organ Toxicity

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“Immuno-ablative Therapeutic Intervals”

Fraction of Non-Engrafted Patients

- Hemoglobinopathies/ e.g. Thalassemia, SCA
- Immunocompetent Pat.

Systemic Drug Exposure

- “Safe Upper Limit”, Syst. Exposure
- aGVHD
- Normal Organ Toxicity

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Fact: You cannot, must not, shall not use chemotherapy to weaken the Immune System in patients/children who do not have a malignant disease.

BUT,

We need to safely, effectively weaken the Immune system and augment immunosuppression to assure stable engraftment and achieve long-term disease control.

Therefore, we introduced:

Pre-conditioning with PharmacoTherapeutic ImmunoSuppression (PTIS).

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“Immuno-ablative Therapeutic Intervals”

- Hemoglobinopathies/ e.g. Thalassemia, SCA
  - Immunocompetent Pat.

- Thalassemia After PTIS.

- "Safe Upper Limit", Syst. Exposure

- aGVHD

- Normal Organ Toxicity

Proportion of Non-Engrafted Patients vs. Systemic Drug Exposure

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Hemoglobinopathy / Genetic Disease

Thalassemia (Pre-) Transplant Platform

Thalassemia, Haplo-identical SCT

Thalassemia
(Pre-) Transplant Platform

Pharmacologic PreTransplant ImmunoSuppression (PTIS)  Conditioning phase

FLU x 5  DXM x 5  FLU x 5  DXM x 5
Day -68 -66 -64  -40 -38 -36 -21  -14 -12 -10

ATG x 3

FLU x 6
BU x 4

Graft
REST

CY +3 +4

Anurathapan U, BMT 2016;51:803-18
Figure 2. EFS and OS of 31 thalassemia patients undergoing haploidentical hemopoietic stem cell transplantation (haplo-SCT)
Outcomes Haplo-Tx vs others

- Haplo
- Related
- Unrelated
“Immuno-ablative Therapeutic Intervals”

- Hemoglobinopathies/ e.g. Thalassemia, SCA
- Immunocompetent Pat.
- Thalassemia After PTIS.
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Systemic Drug Exposure

Fraction of Non-Engrafted Patients

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“Immuno- ablative Therapeutic Intervals”

- Hemoglobinopathies/ e.g. Thalassemia, SCA
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Fraction of Non-Engrafted Patients vs. Systemic Drug Exposure
“Immuno-ablative Therapeutic Intervals”

Fraction of Non-Engrafted Patients

Hemoglobinopathies/ e.g. Thalassemia, SCA Immunocompetent Pat.

Thalassemia After PTIX

"Safe Upper Limit”, Syst. Exposure

aGVHD

Normal Organ Toxicity

Systemic Drug Exposure

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But, This is NOT a Thalassemia-Specific Haplo-identical SCT Program

- It is a Proof-of-Concept for making allogeneic stem cell transplantation a viable treatment for patients who have a genetically debilitating disease and where an active, or hyperactive, immune system complicates an otherwise curative therapy.
Conclusions
Conditioning = Immunosuppression ??

1. Conditioning

2. Patient (age, gender, CMV, comorbidities...)

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A. N.A.-IV Busulfan-based Conditioning

1. Requires Attention to Details, including Timing and Sequencing of the Drugs.
2. Attention Deficit Attenuates Treatment Results.
3. PK-guidance Optimizes treatment Outcome.
B. Personalized, Optimized Therapy Improves outcome!

3 Patient (age, gender, CMV, comorbidities...)

1 Disease Features Mal vs Non-Mal

2 Graft; level of matching

4 GVHD prophylaxis / therapy: CNI-vs Post-Cy based

5 Supportive Care

6 Conditioning N.A./Bu vs other

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Collaborators

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- EJ Shpall
- C Hosing
- RB Jones
- L Worth
- Y Nieto
- Dean Lee
- S Parmar

*Laboratory:*
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- G Wang
- Y Liu
- Y Li

*Biostatistics:*
- PF Thall

**Ramathibodi Hospital, Bangkok, Thailand:**
- Suradej Hongeng

**Institut Paoli Calmette, Marseille, France:**
- Didier Blaise

**Hopital S:t Antoine, Paris, France:**
- Mohamad Mohty

**U Alberta, Calgary, AB, CA:**
- James Russell

**Cross Cancer Center, Edmonton, AB, CA**
- David Murray

**Karolinska Institute, Stockholm, Sweden:**
- Moustapha Hassan
Questions, Please?

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Back-Up Slides
Figure 5a. Overall Survival – Matched Pairs of Patients (Fixed Dose N=34, number of deaths=15; PK-Guided Dose N=68, number of deaths=29), Kaplan-Meier Estimates with 95% confidence bands

Figure 5b. Progression-Free Survival – Matched Pairs of Patients (Fixed Dose N=34, number of deaths=15; PK-Guided Dose N=68, number of deaths=29), Kaplan-Meier Estimates with 95% confidence bands
“Immuno-ablative Therapeutic Intervals”

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