Outline

• Conditioning regimens
  • Definitions & background
• Important questions
• Case studies
• Last requests?
Transplant conditioning regimens

• Myeloablative conditioning regimens
  • Combination of agents expected to produce irreversible (or close to irreversible) pancytopaenia
  • Stem cell support is required to rescue marrow function and prevent aplasia-related death

• Non-myeloablative conditioning regimens
  • Combination of agents producing minimal cytopaenias with no need for stem cell support

• Reduced intensity conditioning regimens
  • Those not fitting either of above definitions
Allogeneic non-myeloablative stem cell transplantation

Pattern of engraftment vs conventional conditioning

Blood counts:
- Non-myeloablative
- Conventional

Weeks post-transplant:
- 0.5 x 10^9/L
- 0.1 x 10^9/L
Myeloablative regimens

- Based on animal models in 1950s
  - TBI 10Gy
  - Cyclophosphamide 200mg/kg
  - Busulphan 16mg/kg
- Others substituted
  - Melphalan
  - Treosulphan
  - Thiotepa
  - Etoposide
Non-myeloablative & reduced intensity regimens

• Late 1990s
• Increasing use of fludarabine (nucleoside analogue) & lower dose TBI
• Sufficient immunosuppression to allow engraftment
• Now ~50% of all allogeneic transplants
Regimen examples

Myeloablative
• TBI ≥ 8Gy fractionated
• Busulphan ≥ 8mg/kg (or IV equivalent)
• Melphalan > 150mg/m²
• Examples
  • Cy/TBI, Bu/Cy, Mel 200

Reduced intensity/NMA
• TBI < 8Gy fractionated
• Busulphan < 8mg/kg (or IV equivalent)
• Melphalan ≤ 150mg/m²
• Examples
  • BEAM (upper limit!)
  • FluBu2
  • FluMel
  • FluTBI
Spectrum of Conditioning Regimens

Less aggressive disease eg CLL

More aggressive disease eg AML

Older patients (up to 70yo)

Younger patients (usu <50yo)

Decreasing Reliance on GVT

Increasing Toxicity

Increasing Intensity

Non-myeloablative
Reduced Intensity
Myeloablative

TBI 200 cGy
FLU/CY/ATG
FLU/CY
FLU + BU (low-dose)
FLU + Melphalan
FLU + BU (full-dose)*
FLU + Treosulfan*
BU + CY 120 mg/kg
BU + CY 200mg/kg
BU + CY + Melphalan
TBI 1200-1400 cGy +/- CY, FLU, Thio, Etop

ATG = Antithymocyte globulin
BU = Busulfan
cGy = Centigray
CY = Cyclophosphamide
Etop = Etoposide
FLU = Fludarabine
GVT = Graft-versus-tumor effect
TBI = Total-body irradiation
Thio = Thiopas

* These two regimens have been associated with lower rates of transplant-related mortality compared with standard myeloablative approaches and are often referred to as reduced-toxicity myeloablative regimens.
Trends in Transplants by Transplant Type and Recipient Age*

Older patients

*Transplants for AML, ALL, NHL, Hodgkin Disease, Multiple Myeloma
Conditioning intensity for allogeneic transplants

Count

Age group

Conditioning

RIC

MA

0-15
16-29
30-39
40-49
50-59
60-69
70+

0
50
100
150

ABMTRR Newsletter
November 2013
Database accrual
Transplant numbers continue to increase, with 1,812 ... from the Data Management Resources page on our website, or contact us for more information. www.abmtrr.org
Current regimens in Australia

**Recipients aged 16+**

<table>
<thead>
<tr>
<th>Conditioning regimen</th>
<th>Myeloablative Total</th>
<th>Reduced intensity Total</th>
<th>% + Ab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fludarabine+Melphalan</td>
<td>9</td>
<td>147</td>
<td>21%</td>
</tr>
<tr>
<td>Busulphan+Cyclophosphamide</td>
<td>75</td>
<td>0</td>
<td>36%</td>
</tr>
<tr>
<td>Busulphan+Fludarabine</td>
<td>25</td>
<td>45</td>
<td>51%</td>
</tr>
<tr>
<td>Cyclophosphamide+TBI</td>
<td>63</td>
<td>1</td>
<td>20%</td>
</tr>
<tr>
<td>Cyclophosphamide+Fludarabine</td>
<td>5</td>
<td>40</td>
<td>49%</td>
</tr>
<tr>
<td>Fludarabine+TBI</td>
<td>5</td>
<td>27</td>
<td>19%</td>
</tr>
<tr>
<td>Carmustine+Fludarabine+Melphalan</td>
<td>1</td>
<td>23</td>
<td>79%</td>
</tr>
<tr>
<td>Cyclophosphamide+Fludarabine+TBI</td>
<td>4</td>
<td>14</td>
<td>17%</td>
</tr>
<tr>
<td>Etoposide+TBI</td>
<td>6</td>
<td>0</td>
<td>67%</td>
</tr>
<tr>
<td>Cyclophosphamide+TBI+Thiotepa</td>
<td>3</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>None</td>
<td>0</td>
<td>7</td>
<td>0%</td>
</tr>
<tr>
<td>Other</td>
<td>16</td>
<td>20</td>
<td>36%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>212</strong></td>
<td><strong>324</strong></td>
<td><strong>33%</strong></td>
</tr>
</tbody>
</table>

+ Ab: including anti-T cell antibody therapy
Allogeneic

Allogeneic conditioning protocol aplastic anaemia CYCLOPHOSPHAmide and ATGAM

Allogeneic conditioning protocol aplastic anaemia CYCLOPHOSPHAmide fludarabine and ATGAM

Allogeneic conditioning protocol aplastic anaemia fludarabine CYCLOPHOSPHAmide and alemtuzumab

Allogeneic intermediate intensity conditioning protocol (cord) CYCLOPHOSPHAmide fludarabine thiotepa and total body irradiation (TBI)

Allogeneic myeloablative conditioning protocol (cord) CYCLOPHOSPHAmide fludarabine and total body irradiation (TBI)
Important Questions

• Why are different treatments used?

• Do the different regimens have different impacts on survival?

• What factors influence choice of regimens?
Total Body Irradiation (TBI)

- Reaches privileged sites with/without blood supply
- Rapid administration
- Short t1/2
- Can dose/target adjust
- Shielding of areas
- Split into fractions to reduce toxicity
Total Body Irradiation (TBI)

- Requires planning & capable facilities
- Variations between techniques and devices

- Side effects
  - Marrow suppression
  - Mucositis
  - Skin/gut toxicity
  - Dry eyes/mouth
  - Longer term
    - Normal organ toxicity (cardiac, lung, gonadal)
    - Cataracts
    - Secondary malignancy risk
Alkylating agents

**Busulphan**
- IV vs oral
  - Pharmacokinetics available
- Specific side effects
  - Seizures – prophylaxis
  - Veno-occlusive disease

**Cyclophosphamide**
- Not myeloablative but immunosuppressive
- Specific side effects
  - Haemorrhagic cystitis
  - Cardiac toxicity

**Melphalan**
- Disease activity for specific disease
- Specific side effects
  - Mucositis
T-cell antibodies

• ATG/thymoglobulin
  • Antibodies against T-cell antigens from either horse or rabbit

• Alemtuzumab
  • Monoclonal antibody to CD52
T-cell antibodies

• Aim
  • Reduce risk of graft rejection by residual host T-cells
  • Reduce risk of graft-versus-host disease by donor T-cells

• Use varies dependent on donor/transplant protocol
  • Commonly used in unrelated donor transplants

• Administration
  • Either single day or split over 2-3 days pre-transplant
  • Reactions common
    • Temperatures, rigors, hypotension, rashes
Important Questions

• Why are different treatments used?

• Do the different regimens have different impacts on survival?

• What factors influence choice of regimens?
Autologous transplant protocols

• Disease specific
  • Lymphomas (Hodgkin & non-Hodgkin) BEAM/LACE/BuMel
  • Myeloma Melphalan 200/150/120
  • Germ cell tumours TICE
  • Scleroderma Cy-TBI-ATG

Based on best evidence & activity against specific disease

P = 0.038

Overall Survival (%) vs. Months after Randomization.
Autologous transplant in myeloma

What factors affect conditioning regimen choice?

**Patient**
- Specific disease*
- Disease status & risk*
- Age*
- Comorbidities
- Performance status
- Previous therapies (eg prior auto)

**Donor/Stem cells**
- Type of donor
- Degree of HLA matching
- T depletion or graft manipulation

**Centre experience**

**Regimen-specimen toxicity**
Allogeneic transplant protocols

• Complex interaction of treatments combining
  • Chemoradiotherapy to suppress/eradicate host immune system*
  • Stem cell graft manipulation
  • Immunosuppression
    • Antibody based (eg ATG)*
    • Immunosuppressants (eg cyclosporin, tacrolimus)
    • Chemotherapy (eg methotrexate, cyclophosphamide)

* = conditioning
HSCT PROTOCOL M2a: Cyclophosphamide / IV-Busulfan

| Disease: | AML / MDS / ALL / CML / NHL |
| Transplant type: | Sibling |
| Cell Source: | BM / PBSC |
| GvHD Prophylaxis: | CsA/MTX |

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Days</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>60g/day</td>
<td>30d</td>
<td>IV (bolus)</td>
</tr>
<tr>
<td>Mesna</td>
<td>60g/day</td>
<td>30d</td>
<td>IV (bolus)</td>
</tr>
<tr>
<td>Busulfan</td>
<td>18g/day</td>
<td>30d</td>
<td>IV (bolus)</td>
</tr>
<tr>
<td>Busulfan</td>
<td>30g/day</td>
<td>40d</td>
<td>IV (bolus)</td>
</tr>
</tbody>
</table>

**DAY | THERAPY**
--- | ---
-8Admission | 
-8Admission | 
-7Admission | 
-7Admission | 
-6Statin | 
-7Statin | 
-7Statin | 
-6Statin | 
-5Statin | 
-4Statin | 
-3Statin | 
-2Statin | 
-1Statin | 
1Statin | 
2Statin | 
3Statin | 
4Statin | 
5Statin | 
6Statin | 
7Statin | 
8Statin | 
9Statin | 
10Statin | 
11Statin | 
12Statin | 
13Statin | 
14Statin | 
15Statin | 
16Statin | 
17Statin | 
18Statin | 
19Statin | 
20Statin | 
21Statin | 
22Statin | 
23Statin | 
24Statin | 
25Statin | 
26Statin | 
27Statin | 
28Statin | 
29Statin | 
30Statin | 
31Statin | 
32Statin | 
33Statin | 
34Statin | 
35Statin | 
36Statin | 
37Statin | 
38Statin | 
39Statin | 
40Statin | 
41Statin | 
42Statin | 
43Statin | 
44Statin | 
45Statin | 
46Statin | 
47Statin | 
48Statin | 
49Statin | 
50Statin | 
51Statin | 
52Statin | 
53Statin | 
54Statin | 
55Statin | 
56Statin | 
57Statin | 
58Statin | 
59Statin | 
60Statin | 

*Note: avoid steroids with iv Busulfan*

(Request Cancer Care Pharmacy to ready product before 9.30am. Levels to be done post infusion.)

*Note: If levels need to repeat on day -2, please request Cancer Care Pharmacy to ready product before 930am*
Case study 1

- Giselle
- 36 yo retail worker
- Acute myeloid leukaemia
  - Poor risk cytogenetics including monosomal karyotype
- Rx with Induction 7-3 Ida, then 2x HIDAC
- In complete remission post induction
- No major treatment complications
- No other major comorbidity
- HLA matched sibling and unrelated donors identified
Which of the following is the most appropriate?

A. Because of her excellent response and minimal complications, she should be referred for transplant if/when relapse occurs.

B. Fludarabine/2Gy unrelated donor transplant would be considered standard therapy

C. An autologous transplant offers her the best balance of long-term survival and treatment related toxicity

D. A Busulphan/cyclophosphamide sibling donor transplant has the highest chance of overall long-term survival
Answers

• High risk leukaemias have survival rates usually 10-20%.
• Autologous transplants used as consolidation treatment (especially in EU) but no difference in survival to standard consolidation treatments
• AML – BuCy-based transplant
  • No statistical difference vs CyTBI.
  • ?Difference with Busulphan pharmacokinetic monitoring
• ALL – CyTBI-based transplant
  • No definitive randomised trial data
  • Based on higher rate of CNS disease and better CNS penetration with radiotherapy
  • Registry data suggests similar outcomes
• Is Reduced Intensity or Myeloablative better?
Organ-specific toxicity

Diaconescu et al, Blood 2004
Treatment related mortality

Diaconescu et al, Blood 2004
Myeloablative vs RIC?

Treatment related mortality significantly higher in myeloablative transplant but outweighed by higher relapse risk

Scott et al, JCO 2017
Case study 2

• Steve G
• 64 yo retired teacher
• Follicular lymphoma 2004
  • Multiple lines chemotherapy including 6x R-CHOP with R maintenance
  • Autologous transplant 2013
  • Trial with BTK inhibitor and PD-1 inhibitor with partial response
• Cx - Neuropathy
• Other comorbidities
  • Stable ischaemic heart disease
  • Diabetes on oral hypoglycaemics
  • Ex-smoker 50packyears
  • Bladder cancer 2010
  • Steatohepatitis
• Donor: No matched siblings, 2x10/10 unrelated donors, 2xhaploidentical children
Which of the following is the most appropriate?

A. A prior history of solid tissue cancer means that a stem cell transplant is not possible

B. A reduced intensity unrelated donor transplant is his best chance for long term survival

C. His comorbidities will significantly impact on success on any transplant and therefore any transplant should be declined.

D. A haploidentical transplant from one of his children is standard of care
Answers

• Comorbidities have a significant impact on any transplant outcome
• Formally measuring this can estimate a patient’s mortality from non-relapse related causes & affect choice of conditioning regimen
• Given age, comorbidities and less aggressive disease, a reduced intensity transplant would be recommended
• A fully matched unrelated donor is still currently considered best practice for transplantation (though this may change...)
HCT-Comorbidity Index

- Arrhythmia
- Cardiovascular
- Inflammatory bowel disease
- Diabetes
- Cerebrovascular disease
- Psychiatric
- Hepatic
- Obesity

- Infection
- Rheumatologic
- Peptic ulcer
- Renal
- Pulmonary
- Prior solid tumour
- Heart valve disease
- Age
How important is HCT-CI?

Sorror et al, Blood 2005
Case study 3

- Michelle A
- 53yo physiotherapist
- Aplastic anaemia 2017
  - Failed immunosuppressive Rx
- Now 2\textsuperscript{nd} weekly RBC/platelet transfusions
- 3 admissions last 6 months for life-threatening neutropaenic sepsis
- Currently fit & well supported
- Donor
  - no fully matched siblings or unrelated donors
  - Multiple single mismatched donors
  - Haploidentical brother, parents & children
  - Cord blood units available
Question

• Which of the following is the best advice?

A. Repeat trial of immunosuppressive treatment or thrombopoietin agonist if available

B. Recommend reduced intensity transplant from haploidentical or cord blood donor

C. Suggest continuing best supportive care

D. She would be an ideal candidate for an outpatient based transplant

E. Recommend mismatched donor transplant
Answers

• Gray areas exist for rarer diseases and the evolving edge of transplants
• Usually have disease-specific designed protocols
• Prior to alternative & mismatched donors, experimental/supportive treatments would be standard
• Newer treatments changing face for certain diseases eg CAR-T cells
Specific conditioning protocols for diseases or donors

Aplastic anaemia

- Cyclophosphamide/ATGAM
- Fludarabine/Cyclo/Alemtuzumab

Scleroderma (SCOT trial)
Double Cord RIC transplant

RIC-haploidentical BM transplant
Trends in alternate donor transplants - EBMT

Passweg et al, BMT 2015
# Outpatient transplants in Australia

## Outpatient procedures

<table>
<thead>
<tr>
<th>Component of transplant</th>
<th>Recipient 0-15</th>
<th>Recipient 16+</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autologous</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conditioning</td>
<td>2.2%</td>
<td>17.9%</td>
</tr>
<tr>
<td>Infusion</td>
<td>0</td>
<td>15.5%</td>
</tr>
<tr>
<td>Acute post-transplant care</td>
<td>2.2%</td>
<td>10.9%</td>
</tr>
<tr>
<td><strong>Allo - reduced intensity conditioning</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conditioning</td>
<td>7.7%</td>
<td>40.4%</td>
</tr>
<tr>
<td>Infusion</td>
<td>0</td>
<td>8.0%</td>
</tr>
<tr>
<td>Acute post-transplant care</td>
<td>0</td>
<td>4.9%</td>
</tr>
<tr>
<td><strong>Allo - Myeloablative conditioning</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conditioning</td>
<td>0</td>
<td>3.3%</td>
</tr>
<tr>
<td>Infusion</td>
<td>0</td>
<td>2.8%</td>
</tr>
<tr>
<td>Acute post-transplant care</td>
<td>0</td>
<td>1.4%</td>
</tr>
</tbody>
</table>

Data show the percentage of transplants where more than half of the time for each transplant component was spent as an outpatient.
Summary

• Conditioning is integrated into the overall transplant protocol
• Choice of regimen is based on multiple patient factors, disease and available donors
• Different conditioning regimens may be specific for certain diseases and result in better outcomes
• Understanding different conditioning allows better directed care
• Because of evolving evidence, there are differences in practice nationally and internationally
THE ROAD TO SUCCESS is always under construction.

Questions?