Introduction to Clinical Hematopoietic Cell Transplantation (HCT)

George Chen, MD
Thursday, May 03, 2018
Hematopoietic Cell Transplantation (HCT)

The transfer of hematopoietic progenitor and stem cells for therapeutic purposes

- Bone marrow transplant
- Hematopoietic stem cell transplant
- Hematopoietic progenitor cell transplant
- Peripheral blood stem cell transplant
Patient

Chemo ± XRT
Patient

Chemo ± XRT
Patient → Chemo ± XRT → Relapse
Patient

Chemo ± XRT

Relapse

HCT
Allogeneic BMT Survival Outcomes (AML)

- Acute GvHD (15%)
- Infection (10%)
- Other (5%)
- Chronic GvHD, dead (15%)
- Disease relapse (20%)
- Chronic GvHD, alive (15%)
- Alive and well (20%)
A transplant is a bet against the future

Leukemia Therapy

High dose Chemo ± XRT

45%
55%
5%
95%
Genetic Subgroup Analysis: RFS

NPM1+/FLT3 ITD-

Relapse-free Survival (%)

p = 0.71
donor n = 35
no donor n = 92

Others

Relapse-free Survival (%)
p = 0.02
donor n = 45
no donor n = 125

Schlenk R et al, NEJM 2008
MUD Transplantation in Relapsed Patients with Unfavorable Genotype

other strategy n=67

MUD n=37

p<0.0001
Prognostic categories for AML

• Good
  – t(8:21), t(9:22), inv16, t(15:17)
  – NPM1
  – CEPB

• Medium
  – Normal karyotype

• Poor
  – Multiple karyotypic abnormalities
  – Flt3 ITD or TDK

• Clinical factors indicating a poor prognosis
  – Induction failure, relapsed disease
  – Prior hematologic disorder
Important Concepts

• Autologous vs allogeneic HCT

• Myeloablative vs reduced intensity conditioning regimens

• Autologous, syngeneic, matched related, matched unrelated, mismatched and haploidentical donors

• Acute vs. chronic graft versus host disease

• Donor chimerism
Basic Definitions

• Autologous HCT – A transplant using a patient’s own cells for the graft.

• Allogeneic HCT – A transplant using another person’s cells for the graft.
Autologous HCT

Patient

Regular Chemo ± XRT

Blood or Marrow Collection

Freezer

High dose Chemo ± XRT

8-14 days
Cytotoxicity vs. Chemotherapy dose

- Linear relationship:
  - Cytotoxicity increases proportionally with chemotherapy dose.

- Non-linear relationship:
  - Cytotoxicity increases to a certain point, then plateaus.

- Dose threshold:
  - Different thresholds for different dosages.
Indications for high dose chemotherapy and autoHCT

• Chemo / radiation dose responsive malignancies
  – Germ cell tumors (testicular)
  – Large cell lymphoma
  – Mantle cell lymphoma (usually)
  – Myeloma

• Replacement of hematopoiesis (rescue therapy)
Patient

Donor

High dose Chemo ± XRT

14-21 days

Time

Regular Chemo ± XRT

Allogeneic HCT
Indications for alloHCT

• Immune mediated effect against the underlying malignancy

• Prevention of relapse
  – Acute and chronic leukemia
  – Myelodysplastic syndrome
  – Indolent lymphomas

• Replacement of hematopoiesis
  – Aplastic anemia
<table>
<thead>
<tr>
<th></th>
<th>Autologous</th>
<th>Allogeneic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Replace hematopoiesis</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Cytoreduction</td>
<td>Yes</td>
<td>Depends</td>
</tr>
<tr>
<td>Immune effect</td>
<td>No *</td>
<td>Yes</td>
</tr>
<tr>
<td>Chemotherapy dose</td>
<td>High</td>
<td>High and low</td>
</tr>
</tbody>
</table>
Important Concepts

- Autologous vs allogeneic HCT
- Myeloablative vs reduced intensity conditioning regimens
- Autologous, syngeneic, matched related, matched unrelated, mismatched and haploidentical donors
- Acute vs. chronic graft versus host disease
- Donor chimerism
Allogeneic BMT

Patient

Donor

Regular Chemo ± XRT

High dose Chemo ± XRT

14-21 days

Time
Allogeneic BMT

Regular Chemo ± XRT

High dose Chemo ± XRT

14-21 days

Time
Non-myeloablative Reduced Intensity AlloBMT
1st CR
MRD
9/10 MUD
All patients

41-60 y/o

18-40 y/o
Transplant regimens

Allo Non-myeloablative
- Flu-Cy
- Flu-Cy-ATG
- Flu-low dose TBI
- Flu ATG
- TLI/ATG
- FLU/CY/TBI 200 cGy

Allo Reduced Intensity
- Flu-Mel
- Flu-Bu
- Flu-Mel-TBI 400 cGy

Auto and Allo Myeloablative
- Cy-TBI 1200 cGY
- Bu-Cy
- Mel 200

More Relapse
More Regimen Related Toxicity

Later Graft-versus Disease Effect
Earlier Anti-Disease Effect

Myelosuppression
Bu, Mel, full dose TBI (~12 Gy)
Bu, Mel, full dose TBI

Fludarabine
Cyclophosphamide

4-hydroxy-cyclophosphamide

Tautomerization

Aldophosphamide

Cytochrome P450

Elevated in stem cells
Higher in resting lymphocytes versus activated lymphocytes

Aldehyde dehydrogenase

Carboxyphosphamide (inactive)

Phosphoramidemustard (active)

Acrolein (active)
<table>
<thead>
<tr>
<th></th>
<th>Auto</th>
<th>Allo RIC</th>
<th>Allo MA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Replace hematopoiesis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Cytoreduction</td>
<td>Yes</td>
<td>Some</td>
<td>Theoretically more</td>
</tr>
<tr>
<td>Immune effect</td>
<td>No *</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Chemotherapy dose</td>
<td>High</td>
<td>Less</td>
<td>More</td>
</tr>
<tr>
<td>Patient toxicity</td>
<td>Yes</td>
<td>Less</td>
<td>More</td>
</tr>
</tbody>
</table>
Important Concepts

• Autologous vs allogeneic HCT
• Myeloablative vs reduced intensity conditioning regimens
• Autologous, syngeneic, matched related, matched unrelated, mismatched and haploidentical donors
• Acute vs. chronic graft versus host disease
• Donor chimerism
Human Leukocyte Antigen (HLA)

• Proteins which present antigenic peptides to T cells
• On surface of most body cells
• The most important proteins in transplant
• Responsible for graft rejection and GvHD
HLA

- Class I – A, B, C
- Class II – DR, DQ, DP
**HLA**

- $(>1 \times 10^{12} \text{ haplotypes})^2 = > 1 \times 10^{24} \text{ combinations}$
- Frequencies are not equal distributed
- Not all alleles have been identified

<table>
<thead>
<tr>
<th>HLA</th>
<th>DRB1</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>DQB1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alleles</td>
<td>400</td>
<td>370</td>
<td>660</td>
<td>190</td>
<td>62</td>
</tr>
</tbody>
</table>
HLA Inheritance

Chance of a matched sibling = $1 - 0.75^\# \text{ of other siblings}$

Haplotype – the set of HLA genes inherited from one parent
Matched Donor
6/6 HLA Matched

<table>
<thead>
<tr>
<th>Maternal haplotype</th>
<th>Paternal haplotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRB1</td>
<td>DRB1</td>
</tr>
<tr>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>DQ</td>
<td>DQ</td>
</tr>
<tr>
<td>DP</td>
<td>DP</td>
</tr>
</tbody>
</table>

Donor

<table>
<thead>
<tr>
<th>Recipient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal haplotype</td>
</tr>
<tr>
<td>DRB1</td>
</tr>
<tr>
<td>B</td>
</tr>
<tr>
<td>A</td>
</tr>
<tr>
<td>C</td>
</tr>
<tr>
<td>DQ</td>
</tr>
<tr>
<td>DP</td>
</tr>
</tbody>
</table>
Matched Donor
8/8 HLA Matched

<table>
<thead>
<tr>
<th>Donor</th>
<th>Recipient</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maternal haplotype</strong></td>
<td><strong>Paternal haplotype</strong></td>
</tr>
<tr>
<td>DRB1</td>
<td>DRB1</td>
</tr>
<tr>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>DQ</td>
<td>DQ</td>
</tr>
<tr>
<td>DP</td>
<td>DP</td>
</tr>
</tbody>
</table>
**Matched Donor**
10/10 matched

<table>
<thead>
<tr>
<th>Maternal haplotype</th>
<th>Paternal haplotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRB1</td>
<td>DRB1</td>
</tr>
<tr>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>DQ</td>
<td>DQ</td>
</tr>
<tr>
<td>DP</td>
<td>DP</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Maternal haplotype</th>
<th>Paternal haplotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRB1</td>
<td>DRB1</td>
</tr>
<tr>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>DQ</td>
<td>DQ</td>
</tr>
<tr>
<td>DP</td>
<td>DP</td>
</tr>
</tbody>
</table>
Matched **Un**Related Donor
10/10 HLA matched DP matched
12/12 HLA Matched

<table>
<thead>
<tr>
<th>Donor</th>
<th>Recipient</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maternal haplotype</strong></td>
<td><strong>Paternal haplotype</strong></td>
</tr>
<tr>
<td>DRB1</td>
<td>DRB1</td>
</tr>
<tr>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>DQ</td>
<td>DQ</td>
</tr>
<tr>
<td>DP</td>
<td>DP</td>
</tr>
</tbody>
</table>
Haploidentical Donor
3/6 HLA matched
Anything ≤4/6 HLA matched

<table>
<thead>
<tr>
<th>Maternal haplotype</th>
<th>Paternal haplotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRB1</td>
<td>DRB1</td>
</tr>
<tr>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>DQ</td>
<td>DQ</td>
</tr>
<tr>
<td>DP</td>
<td>DP</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Maternal haplotype</th>
<th>Paternal haplotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRB1</td>
<td>DRB1</td>
</tr>
<tr>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>DQ</td>
<td>DQ</td>
</tr>
<tr>
<td>DP</td>
<td>DP</td>
</tr>
</tbody>
</table>
A antigen mismatched donor

<table>
<thead>
<tr>
<th>Donor</th>
<th>Recipient</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maternal haplotype</strong></td>
<td><strong>Maternal haplotype</strong></td>
</tr>
<tr>
<td>DRB1-1</td>
<td>DRB1-1</td>
</tr>
<tr>
<td>B-1</td>
<td>B-1</td>
</tr>
<tr>
<td>A-1</td>
<td>A-1</td>
</tr>
<tr>
<td>C-1</td>
<td>C-1</td>
</tr>
<tr>
<td>DQ-1</td>
<td>DQ-1</td>
</tr>
<tr>
<td>DP-1</td>
<td>DP-1</td>
</tr>
</tbody>
</table>
A antigen mismatched donor

## Recipient

<table>
<thead>
<tr>
<th>Maternal haplotype</th>
<th>Paternal haplotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRB1-1</td>
<td>DRB1-2</td>
</tr>
<tr>
<td>B-1</td>
<td>B-2</td>
</tr>
<tr>
<td>A-1</td>
<td>A-2</td>
</tr>
<tr>
<td>C-1</td>
<td>C-2</td>
</tr>
<tr>
<td>DQ-1</td>
<td>DQ-2</td>
</tr>
<tr>
<td>DP-1</td>
<td>DP-2</td>
</tr>
</tbody>
</table>

## Donor

<table>
<thead>
<tr>
<th>Maternal haplotype</th>
<th>Paternal haplotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRB1-1</td>
<td>DRB1-2</td>
</tr>
<tr>
<td>B-1</td>
<td>B-2</td>
</tr>
<tr>
<td>A-3</td>
<td>A-2</td>
</tr>
<tr>
<td>C-1</td>
<td>C-2</td>
</tr>
<tr>
<td>DQ-1</td>
<td>DQ-2</td>
</tr>
<tr>
<td>DP-1</td>
<td>DP-2</td>
</tr>
<tr>
<td>Recipient</td>
<td>Donor</td>
</tr>
<tr>
<td>-----------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Maternal haplotype</td>
<td>Paternal haplotype</td>
</tr>
<tr>
<td>DRB1</td>
<td>DRB1</td>
</tr>
<tr>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>DQ</td>
<td>DQ</td>
</tr>
<tr>
<td>DP</td>
<td>DP</td>
</tr>
</tbody>
</table>

HLA Expression Level

• High expression level (HEL) antigens – DRB1, A, B, C
• Low expression level (LEL) antigens – DQ, DP, DRB3-5
**MisMatched UnRelated Donor**
**High vs Low Expression Level Antigens**

<table>
<thead>
<tr>
<th>Recipient</th>
<th>Donor</th>
<th>Donor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal haplotype</td>
<td>Paternal haplotype</td>
<td>Maternal haplotype</td>
</tr>
<tr>
<td>DRB1</td>
<td>DRB1</td>
<td>DRB1</td>
</tr>
<tr>
<td>B</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>DQ</td>
<td>DQ</td>
<td>DQ</td>
</tr>
<tr>
<td>DP</td>
<td>DP</td>
<td>DP</td>
</tr>
</tbody>
</table>

### Relative degree of mismatch

<table>
<thead>
<tr>
<th>Recipient</th>
<th>Donor</th>
<th>Donor</th>
<th>Donor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maternal haplotype</strong></td>
<td><strong>Paternal haplotype</strong></td>
<td><strong>Maternal haplotype</strong></td>
<td><strong>Paternal haplotype</strong></td>
</tr>
<tr>
<td>DRB1</td>
<td>DRB1</td>
<td>DRB1</td>
<td>DRB1</td>
</tr>
<tr>
<td>B</td>
<td>B</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>DQ</td>
<td>DQ</td>
<td>DQ</td>
<td><strong>DQ</strong></td>
</tr>
<tr>
<td>DP</td>
<td>DP</td>
<td>DP</td>
<td>DP</td>
</tr>
</tbody>
</table>

The table above illustrates the relative degree of mismatch between different haplotypes. The mismatch is indicated by the red color, where a red cell indicates a mismatch. For example, in the Recipient and Donor columns, the DRB1 haplotype mismatch between B and B is not highlighted, whereas the mismatch between A and A is highlighted.
Donor Selection

- Human leukocyte antigen (HLA) matching
- Relatedness
- Cytomegalovirus status
- Age
- Gender (parity)
- Not blood ABO type
Important Concepts

• Autologous vs allogeneic HCT
• Myeloablative vs reduced intensity conditioning regimens
• Autologous, syngeneic, matched related, matched unrelated, mismatched and haploidentical donors
• Acute vs. chronic graft versus host disease
• Donor chimerism
Immunologic Effects of Allogeneic Grafts

• Graft-versus-Tumor Effects – Reaction of the donor immune system against the recipient’s malignancy

• Graft-versus-Host Effects – Reaction of the donor immune system against the recipient’s body tissues.

• Different sides of the same coin.
Probability of Relapse After 2,254 HLA-identical Sibling Transplants for Early Leukemia

- Twins (N=70)
- T Cell Depletion (n=401)
- No GVHD (n=433)
- AGVHD Only (n=738)
- CGVHD Only (N=127)
- AGVHD + CGVHD (N=485)

Increasing GVT

Increasing GVH
Prevention/Control of aGvHD Is Important

<table>
<thead>
<tr>
<th>Acute GvHD</th>
<th>100 Day Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>78-90%</td>
</tr>
<tr>
<td>Grade II</td>
<td>66-92%</td>
</tr>
<tr>
<td>Grade III</td>
<td>29-62%</td>
</tr>
<tr>
<td>Grade IV</td>
<td>23-25%</td>
</tr>
</tbody>
</table>

(Przepiorka et al, 1995)
Acute GvHD

- Reaction of donor’s immune system against the recipient’s body tissues
- Manifests as diarrhea, skin rash, liver test abnormalities usually within the first 100 days.
- ~20-50% of allogeneic transplants will develop some aGvHD
- Associated with a 15-20% mortality
• Prophylaxis – Prevention of aGvHD
• Treatment – Therapy of aGvHD
Allogeneic BMT

- Regular Chemo ± XRT
- High dose Chemo ± XRT

Donor

Patient

14-21 days

Time
Acute GvHD Prophylaxis

• Micro methotrexate
• Post transplant cyclophosphamide
• Alpha beta T cell depletion and CD34 selection
Billingham Criteria (1966)

• The graft must contain immunologically competent cells

• The host must possess important transplantation alloantigens that are lacking in the donor graft, so that the host appears foreign to the graft, and is, therefore, capable of stimulating it antigenically

• The host itself must be incapable of mounting an effective immunological reaction against the graft, at least for sufficient time for the latter to manifest its immunological capabilities; that is, it (the graft) must have the security of tenure
Cyclophosphamide

\[ \text{Cytochrome P450} \]

4-hydroxy-cyclophosphamide

\[ \text{Tautomerization} \]

Aldophosphamide

\[ \text{Aldehyde dehydrogenase} \]

Carboxyphosphamidamide (inactive)

\[ \text{Acrolein} \text{ (active)} \]

Elevated in stem cells

Higher in resting lymphocytes versus activated lymphocytes
Day -6 -5 -4 -3 -2 -1 0 1 2 3 4 5 6 7 8

↑ ↑ ↑ ↑ ↑ ↑ ↑
FLU-CY-TBI

TAC and MMF

↓ MMF and tacrolimus
↓ High dose CY
↓ Graft
MMF and tacrolimus

High dose CY

Graft

Day

-6 -5 -4 -3 -2 -1 0 1 2 3 4 5 6 7 8

TAC and MMF

FLU-CY-TBI

- MMF and tacrolimus
- High dose CY
- Graft

(With arrows indicating the timeline and medications)
MMF and tacrolimus

High dose CY

Graft

Day

-6 -5 -4 -3 -2 -1 0 1 2 3 4 5 6 7 8

T cell proliferation

TAC and MMF

FLU-CY-TBI

- MMF and tacrolimus
- High dose CY
- Graft
T cell proliferation

Day

FLU-CY-TBI

TAC and MMF

MMF and tacrolimus
High dose CY
Graft
T cell proliferation

Day: -6 -5 -4 -3 -2 -1 0 1 2 3 4 5 6 7 8

TAC and MMF

FLU-CY-TBI

CY

MMF and tacrolimus
High dose CY
Graft

Graft
Post HCT cyclophosphamide (Cy) for GvHD
Post HCT cyclophosphamide (Cy) for GvHD
Post HCT cyclophosphamide (Cy) for GvHD
Post HCT cyclophosphamide (Cy) for GvHD
Post HCT cyclophosphamide (Cy) for GvHD
Post HCT cyclophosphamide (Cy) for GvHD
Post HCT cyclophosphamide (Cy) for GvHD
Acute GvHD Prophylaxis

- Micro methotrexate
- Post transplant cyclophosphamide
- Alpha beta T cell depletion and CD34 selection
Billingham Criteria (1966)

• The graft must contain immunologically competent cells

• The host must possess important transplantation alloantigens that are lacking in the donor graft, so that the host appears foreign to the graft, and is, therefore, capable of stimulating it antigenically

• The host itself must be incapable of mounting an effective immunological reaction against the graft, at least for sufficient time for the latter to manifest its immunological capabilities; that is, it (the graft) must have the security of tenure
αβ T Cell Depletion
αβ T Cell Depletion
αβ T Cell Depletion

Patient
αβ T Cell Depletion
αβ T Cell Depletion

WASTE
CD34+ Cell Selection
CD34+ Cell Selection
CD34+ Cell Selection
CD34+ Cell Selection

WASTE
CD34+ Cell Selection
CD34+ Cell Selection

Patient
<table>
<thead>
<tr>
<th></th>
<th>Ab-TCD</th>
<th>Pt-Cy</th>
<th>uMTX</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active agent</strong></td>
<td>Clinimacs</td>
<td>Cyclophosphamide</td>
<td>Methotrexate</td>
</tr>
<tr>
<td><strong>Target</strong></td>
<td>Alpha beta T cells</td>
<td>Proliferating T cells</td>
<td>Proliferating T cells</td>
</tr>
<tr>
<td><strong>Place of action</strong></td>
<td>Ex vivo</td>
<td>In vivo</td>
<td>In vivo</td>
</tr>
<tr>
<td><strong>T cell</strong></td>
<td>Depletion</td>
<td>Depletion</td>
<td>Inhibition</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>Tacro</td>
<td>Tacro Cellcept</td>
<td>Tacro Cellcept</td>
</tr>
</tbody>
</table>
Probability of Relapse After 2,254 HLA-identical Sibling Transplants for Early Leukemia

- Twins (N=70)
- T Cell Depletion (n=401)
- No GVHD (n=433)
- AGVHD Only (n=738)
- CGVHD Only (N=127)
- AGVHD + CGVHD (N=485)
Chronic Graft-versus-Host Disease

• Post transplant complication usually occurring > 100 days characterized by
  – Fibrotic skin disease
  – Dry and gritty mouth eyes due to glandular destruction
  – Gastrointestinal fibrosis with malnutrition

• 50% of long term survivors will develop some form of cGvHD

• Chronic GvHD is the major cause of long term mortality other than relapse after transplant