Bone Marrow Transplantation and malignant haematology

Jeff Szer
Clinical Haematology at PeterMac and The Royal Melbourne Hospital

@marrow
Tips for haematological malignancies

• Splenomegaly
  • Never see in myeloma
  • In AML confined to monocytic leukaemias
    • Don’t forget the gums (and potassium)
  • Common in MPNs
  • Thrombocytopenia may not be real

• Post splenectomy changes
  • Howell-Jolly bodies
  • Target cells
More tips: genes

• CML
  • BCR-ABL Philadelphia chromosome: t(9;22)
• MPN
  • JAK2 and CALR
• AML
  • FLT3, NPM1
  • t(15;17): PML-RARα
    • Coagulopathy
    • Differentiation syndrome
  • inv(16), t(8;21): core-binding-factor mutations
• ALL
  • Philadelphia chromosome
Some more random tips

• Myeloid cells are stickier than lymphoid cells
  • Rarely will see hyperviscosity from intense lymphocytosis

• IgM > IgA >> IgG for hyperviscosity

• Hyperkalaemia in an asymptomatic patient with very high leukocyte count
  • Time on bench
Transplant types

• Donor source
  • Allogeneic
    • HLA-identical sibling
    • HLA-matched unrelated volunteer donor
    • Haploidentical family member donor
  • Stem cell source:
    • Peripheral blood derived
    • Bone marrow
    • Umbilical cord blood
• Autologous
  • Almost 100% peripheral blood
It all started here
Difference between allogeneic and autologous transplants

• Autologous transplants are simply a vehicle for delivering highly marrow-toxic therapy
  • Myeloma
  • NHL and HL
  • Rarely, specific solid tumours (germ cell, small round cell)

• Allogeneic transplants
  • High dose therapy
  • Also reduced-intensity
  • Graft-versus-host disease: T lymphocyte driven
    • Immunotherapy
      • CML>AML>ALL
      • FL=MCL=CLL>>DLBCL (except Primary Mediastinal)
Timing and planning of allogeneic transplants

• Important to understand patient eligibility and timing
  • Stable disease
  • Appropriate time in disease process

• Pre-transplant involvement
  • Ensure treatments given do not preclude transplant
  • Allow patients to move quickly to transplant if needed, prior to disease progression or development of complications
  • Allow adequate time for donor search if needed.
Day 0

Conditioning

Conditioning regimen
- intensity
- chemotherapy
- radiotherapy
- T cell depletion
- Immuno-manipulation

Immunosuppression

Donor and product variables
- Sibling
- MUD
- CORD
- Haplo-identical
- Donor derived cellular therapies

Cells

Donor derived cellular therapies

Patient variables
- Comorbidities
- Psychology
- Sociology

Psychology

Past treatments

Late Effects

Engraftment

Post transplant maintenance strategies
- Immuno-manipulation
- Treatment of GVHD

Conditioning regimen intensity chemotherapy radiotherapy T cell depletion Immuno-manipulation

Sociology

Conditioning

Immunosuppression
ANATOMY OF AN ALLOGRAFT

Early Complications = Sepsis, opportunistic infections, Mucositis, Fluid Balance, Drug tox (VOD)

Late Tox = opportunistic infection

Acute GVHD

Chronic GVHD

Relapse

Past treatments

Day 0  Day 100
Who gets what?

• Patients with active and especially refractory disease (except for MDS and MF) rarely are offered transplant
  • Exception: autologous transplant for myeloma

• Patients with bone marrow failure are not eligible for autologous transplants (obvious)

• Poorer risk leukaemias do worse after transplant as well

• The earlier in the course of treatment a transplant is done
  • Less toxicity
  • Greater chance of disease control
  • Most difficulty with risk/benefit
Who gets what?

• Autologous transplants for myeloma
  • Early in disease course
  • Improve survival and QOL
  • Non curative

• Autologous transplants for lymphoma (inc Hodgkin)
  • After salvage therapy
  • Curative intent

• Allogeneic transplants
  • Always with curative intent
Graft versus host disease

• Donor T cell driven
  • But not as simple as that

• Acute
  • In first 100 days traditionally
    • Skin liver and gut
    • Prophylaxis:
      • Tissue typing (blood groups largely irrelevant
      • Ciclosporin/MTX; ATG; Post-transplant cyclophosphamide (PTCy)

• Treatment
  • Corticosteroids
Graft versus host disease

- Chronic
  - Generally after day 100
  - The major impediment to Karnofsky score of 100
- Risk factors:
  - Prior acute GVHD
  - Older donors
  - Peripheral blood derived stem cell source
- Target organs
  - All (kidneys extremely rare)
  - Looks like many autoimmune diseases (but is alloimmune)
- Treatment
  - Corticosteroids
What might you see?

- Graft versus host disease
  - Skin: dry, itchy, dyspigmentation, sclerodermatous
  - Oral: ulceration, lichenoid
  - Liver: usually tests only
  - Gut: chronic diarrhoea, malnutrition, pancreatic insufficiency
  - Ocular: dry eyes, cataracts
  - Lungs: Bronchiolitis Obliterans
  - Effects of ongoing immunosuppression: steroids ± …..

- Remember infection risk and effective post-splenectomy state
  - Secondary immunoglobulin deficiency
  - Lymphopoenia
# AML Prognostic Risk Groups

*Based on Cytogenetic Risk and Molecular Profile (NCCN Guidelines)*

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Cytogenetic Profile</th>
<th>Molecular Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable</td>
<td>Core binding factor (CBF): t(8;21)* or inv(16)* or t(16;16) t(15;17)</td>
<td>Normal cytogenetics: Mutated NPM1 without FLT3-ITD or isolated mutated biallelic CEBPA</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Normal cytogenetics trisomy 8 alone t(9;11) Other non-defined</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>Complex (≥ 3 clonal chromosomal abnormalities) Monosomal karyotype del 5, 5q, del 7, 7q 11q23 – non t(9;11) inv(3), t(3;3) t(6;9), t(9;22)</td>
<td>Cytogenetically normal (CN) with FLT3-ITD TP53 mutation</td>
</tr>
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</table>

*Emerging data indicate that the presence of c-KIT mutations in patients with t(8:21), and to a lesser extent inv(16), confers a higher risk of relapse. These patients are considered intermediate risk and should be considered for clinical trials, if available.*
Timing for HCT Consultation

Adult Leukemias and Myelodysplasia

Acute Myelogenous Leukemia (AML) - Adult

High-resolution HLA typing is recommended at diagnosis for all patients

Early after initial diagnosis, all AML patients including:

- CR1 — except favorable risk AML [defined as: t(16;16), inv 16, or t(8;21) without c-KIT mutation; t(15;17); normal cytogenetics with NPM1 or isolated biallelic CEBPA mutation and without FLT3-ITD]
- Antecedent hematological disease (e.g., myelodysplastic syndrome (MDS))
- Treatment-related leukemia
- Primary induction failure or relapse
- Presence of minimal residual disease after initial or subsequent therapy
- CR2 and beyond, if not previously evaluated
Transplantation Timing Matters

**Early Stage**

**Intermediate Stage**

**Late Stage**

Patients transplanted earlier in their disease have better outcomes than patients with advanced disease, regardless of the degree of match.

Overall Survival by Disease Group

**MDS (N=54)**
- **RIC 85.2%**
- **MAC 81.5%**
- **P=0.71 (18 month pointwise)**

**AML (N=218)**
- **RIC 63%**
- **MAC 76.8%**
- **P=0.027 (18 month pointwise)**
Treatment-related Mortality

\[ P=0.02 \ (18 \text{ month pointwise}) \]

MAC 15.8%

RIC 4.4%

Timing for HCT Consultation

Adult Leukemias and Myelodysplasia

Acute lymphoblastic leukemia (ALL) – Adult

High-resolution HLA typing is recommended at diagnosis for all patients

Early after initial diagnosis, all ALL patients including:

- CR1
- Primary induction failure or relapse
- Presence of minimal residual disease after initial or subsequent therapy
- CR2 and beyond, if not previously evaluated
HCT for Myeloproliferative Neoplasm

- Most of the outcome data are from retrospective studies and relate to HCT for primary myelofibrosis or myelofibrosis (MF) evolved from other myeloproliferative neoplasms.
- DIPSS has as been validated as predictor for post-HCT outcomes.
- DIPSS independent factors - karyotype (DIPSS plus) and gene mutation profile (JAK2/MPL/CALR or ASXL1) may also be valuable for decision making.
- No prospective HCT versus non-HCT comparative studies.
HCT for Myeloproliferative Neoplasm

- In the largest study (n=438) outcomes with allo-HCT versus non-HCT approach were compared in primary MF patients grouped by DIPSS status.
- DIPSS intermediate-2 or high risk patients clearly benefited from HCT. Low risk did better with non-HCT approach. Intermediate-1 had similar survival with the two approaches.
- Caveats:
  - Only patients with primary MF were included
  - Ruxolitinib was not used
  - All patients were < 65 years old

HCT for Myeloproliferative Neoplasm

• Generally accepted indications:
  • Primary Myelofibrosis DIPSS Int-2 or High Risk
  • High Risk karyotype and gene profile (even with low risk DIPSS)
  • AML after MF
  • Secondary MF after ET or PV
  • ELN: < 5 years expected survival

• The balance of risk versus benefit has to be assessed for each patient individually.

• Early referral is strongly advocated to allow optimal patient selection and timing to ensure the highest likelihood of benefiting from HCT
Survival after HLA-Matched Sibling Donor HCT for MPNs, 2004-2014

Probability, %

Years

Myelofibrosis (n=631)

Other MPN (n=770)

p=0.009

Survival after Allogeneic HCT for Chronic Lymphocytic Leukemia (CLL), 2004-2014

- HLA-Matched Sibling (n=1,282)
- Unrelated Donor (n=1,693)

p < 0.001

# ASBMT Recommendations for HCT in Non-Hodgkin Lymphoma

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Grade of Recommendation</th>
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<tbody>
<tr>
<td>➢ ASCT is not recommended as first-line therapy except for high IPI group.</td>
<td>A</td>
</tr>
<tr>
<td>➢ ASCT is not recommended for pts who achieve PR to abbreviated (3 cycles) induction regimen.</td>
<td>A</td>
</tr>
<tr>
<td>➢ ASCT is recommended as part of salvage therapy for pts with chemosensitive relapsed DLBCL.</td>
<td>A</td>
</tr>
<tr>
<td>➢ Older age (&gt;60 years) is not a contraindication for ASCT.</td>
<td>B</td>
</tr>
<tr>
<td>➢ OS outcomes are equivalent for ASCT and Allo-HCT; they have competing risks with regard to relapse and TRM; neither option is recommended over the other.</td>
<td>N/A</td>
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<td>PBSC is the standard for stem cell source for ASCT.</td>
<td>A</td>
</tr>
<tr>
<td>Rituximab maintenance is not recommended post ASCT.</td>
<td>A</td>
</tr>
<tr>
<td>There are insufficient data to make a treatment recommendation regarding number of cycles of induction therapy prior to first-line autologous SCT.</td>
<td>N/A</td>
</tr>
<tr>
<td>Planned tandem ASCT is not recommended.</td>
<td>B</td>
</tr>
<tr>
<td>RIC appears to be an acceptable alternative approach for pts who cannot tolerate a myeloablative regimen.</td>
<td>N/A</td>
</tr>
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Survival after Autologous HCT for Follicular Lymphoma, 2004-2014

Survival after Allogeneic HCT for Follicular Lymphoma, 2004-2014

- HLA Matched Sibling, Sensitive (n=854)
- Unrelated Donor, Sensitive (n=721)
- HLA Matched Sibling, Resistant (n=139)
- Unrelated Donor, Resistant (n=157)

p<0.001

Causes of Death after Autologous HCT done in 2013-2014

Causes of Death after Unrelated Donor HCT done in 2013-2014

Died within 100 days post-transplant:
- Primary Disease: 34%
- GVHD: 23%
- Graft Rejection: 11%
- Infection: 10%
- Organ Failure: 2%
- Other: 2%

Died at or beyond 100 days post-transplant:
- Primary Disease: 27%
- GVHD: 46%
- Infection: 6%
- Organ Failure: 10%
- Secondary Malignancy: 9%
- Hemorrhage: 1%
- Other: 1%
Conclusions

• In the current era, almost all patients will have a suitable donor

• Optimal timing of HCT is critical to good outcomes

• Early referral to the transplant center ensures that the RIGHT patient gets transplanted at the RIGHT time with the BEST graft source

• Post transplant survivors are at risk for early and late complications months to years following HCT and need ongoing screening, preventive care and follow up