Indications and Complications of Bone Marrow Transplantation (BMT)

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RBWH
Perspective is important ......
My perspective……..

- Clinical BMT specialist at RBWH
- Moderately large BMT unit
- Perform ~120 SCT / yr
RBWH BMT Unit

120 transplants per year

2/3 allo

- 60% Acute Leukaemia
- 16% NHL
- 8% MDS
- 7% Chronic Leukaemia
- 5% Myeloma
- 5% other (SAA, Hodgkin’s)

1/3 auto

- 37% NHL
- 37% Myeloma
- 14% Hodgkin’s lymphoma
- 12% Solid Tumors
Agenda

- Types of haematopoietic progenitor (stem) cell transplants
  - Autologous
  - Allogeneic

- Complications of transplantation
  - Autologous
  - Allogeneic

- Disease-specific indications for SCT
  - Acute leukaemia: AML / ALL
  - MDS
  - Chronic leukaemia: CML, CLL
  - NHL
  - Hodgkins
  - Myeloma / amyloidosis
Autologous SCT

- Re-infuse pre-stored recipient stem cells to support high dose chemo / radiotherapy
- Requires prior collection and cryopreservation of autologous stem cells
Autologous SCT

- Traditionally, bone marrow used as stem cell source
  - Small number of stem cells
  - Harvesting relatively painful

- Now almost exclusively use peripheral blood progenitor cells (PBPC)
  - "Mobilised" from bone marrow using G-CSF +/- chemotherapy
  - Collected using cell separator / apheresis
Apheresis Procedure
Dose-response relationship

Dose of Therapy

Tumour Response (Killing)

Lethal Dose to Bone Marrow

Lethal Dose to Other organs
Dose-response relationship

Dose of Therapy

Lethal Dose to Bone Marrow

Lethal Dose to Other organs

Tumour Response (Killing)
Common conditioning (preparative) regimens

- Radiation-based
  - Cy / TBI
    - Many series associated TBI with increase risk 2\textsuperscript{nd} MDS / AML

- Chemotherapy-based
  - BEAM (BCNU / etoposide / cytarabine / melphalan)
    - +/- rituximab (anti-CD20 mAb)
    - Lymphoma
  - BuMelT (busulphan / melphalan / thiotepa)
    - Lymphoma
  - HDM (melphalan)
    - Myeloma
  - ICE (ifosfamide / carboplatin / etoposide)
    - Germ cell tumors
Autologous SCT

- Conditioning regimen
- Neutropenic period (10-14 days)
- SC re-infusion (D0)
- Post-engraftment period
Autologous SCT

Conditioning regimen

Neutropenic period (10-14 days)

SC re-infusion (D0)

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Conditioning regimen  Neutropenic period (10-14 days)

SC re-infusion (D0)  Post-engraftment period
Autologous SCT

Conditioning regimen → Neutropenic period (10-14 days)

SC re-infusion (D0) → Post-engraftment period
<table>
<thead>
<tr>
<th>Conditioning / neutropenic</th>
<th>1-3mths</th>
<th>&gt;3mths</th>
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<tbody>
<tr>
<td>Conditioning-related toxicity</td>
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<td>Mucositis</td>
<td>Anorexia</td>
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<td>VOD</td>
<td>Fatigue</td>
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<td>Bacterial enteric GN / line related</td>
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<td>Fungal</td>
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<td>Viral</td>
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<td>HSV</td>
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<td>Infertility</td>
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<td>2nd malignancy</td>
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<td></td>
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<td>2nd MDS / AML</td>
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<td>solid organ cancer</td>
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Limitation of AutoSCT’s

- Does not overcome other (non-bone marrow) toxicities
  - Alopecia
  - Mucosal toxicity e.g. oropharynx, gut
  - Liver (VOD)
- Moderate risk of mortality ~5%
- Cannot cure tumours not otherwise cured by chemotherapy
  - Myeloma
  - Indolent lymphomas, CLL
- Risk of tumor-contamination of autologous stem cell product (at collection / mobilization)
  - Contribute to later relapse
Autologous SCT

- **Post-engraftment issues**
  - Immune reconstitution
    - Infection
  - Endocrine issues
    - Infertility
      - Women invariably ovarian failure
      - Men impaired spermatogenesis (raised FSH / Sertoli cell damage) but testosterone deficiency relatively uncommon

- **2nd malignancies**
  - 2nd MDS / AML
  - Solid tumors
Autologous SCT – immune reconstitution

Traditionally:
- Ig levels recover after 2-3mths
- CD4+ T-cell numbers recover 3-9mths

Addition of monoclonal antibodies (rituximab)
- Depletion of CD27+ memory B-cells
- Acquired CVID-type phenotype

Associated
- Abnormal B-cell repertoires
- Prolonged hypogammaglobulinaemia 30-40% up to 1-2yrs

BJH 2007; 137; 349; EJH 2006; 77: 226; BMT 2006; 38: 433
Autologous SCT – infection

- Main infection risk in medium term VZV reactivation
  - 20-40% reactivate in 1st 12mths
  - Prolonged prophylaxis only delays onset (doesn’t prevent)
Autologous SCT - vaccinations

- Start vaccinations at 12mths
  - Inactivated polio vaccine (eIPV)
  - Adult tetanus/diphtheria toxoid (ADT)
  - Hepatitis B vaccination
  - Pneumococcal vaccine
  - Haemophilus Influenza Type B Vaccine

- 2 years post transplant
  - Measles, mumps, rubella (MMR - live attenuated vaccine)

- Annually every April
  - Influenza vaccine

- Vaccinations NOT recommended and / or contraindicated
  - Meningococcal vaccine - only consider if risk of meningococcal disease felt to be significantly increased
  - Pertussis vaccine – not recommended
  - BCG vaccination - contraindicated
Autologous SCT – 2nd malignancy

- 2nd MDS / AML
  - Actuarial risk 2-20% at 2-10yrs
  - Risk factors include:
    - No prior therapies
    - Age >35-40yrs
    - PBPC grafts (esp if collected off etoposide)
    - TBI-based conditioning
  - FBC performed at least annually
Autologous SCT – 2\textsuperscript{nd} malignancy

- Solid tumors
  - Increased risk 2-5x
  - Especially breast, lung (smokers) skin and prostate
- Stop smoking and avoid sunburn
- Annual
  - Physical exam (including breast exam)
  - Dermatology review
  - Pap smears + mammograms (age >40) (women)
  - PSA testing (men)
Allogeneic SCT
Rationale 1

- Allogeneic stem cell source
  - Stem cells (graft) comes from someone else (healthy donor)
    - Matched family (sibling)
    - Volunteer unrelated donor (VUD)
    - Umbilical cord unit (“cord”)
  - Tumor-free
Rationale 2

- Stem cells (graft) comes from someone else (healthy donor)
  - New immune system
  - Immunotherapy platform to induce potential graft versus malignancy (GVM) effect
    - Side effect new immune system attacks whole host (not just underlying malignancy)
    - Graft vs host disease (GVHD)
GVM effect

- Different malignancies varying responsiveness to GVM effect

- FL / CML
- AML / ALL
- MM / DLCL / Hodgkin’s
Allogeneic SCT

- **Sub-classify**
  - **Donor source**
    - Matched sibling vs VUD vs haploidentical vs cord
  - **Source of stem cells**
    - BM vs primed BM vs PBPC vs cord
  - **Graft manipulation**
    - T-replete vs T-depleted
  - **Conditioning regimen**
    - Myeloablative vs reduced intensity conditioning (RIC)

- **Complications can vary**
Allogeneic SCT

Conditioning regimen

Neutropenic period (0->21 days)

SC re-infusion (D0)

Post-engraftment period
Allogeneic SCT

Conditioning regimen

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Allogeneic SCT

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SC re-infusion (D0)  ALLOGRAFT  Post-engraftment period
Allogeneic SCT

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SC re-infusion (D0)

ALLOGRAFT
- Immunosuppressive therapy
- Recipient rejecting graft
- Graft rejecting recipient (graft vs host disease)
- Delayed immune reconstitution

Post-engraftment period
Allogeneic SCT

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SC re-infusion (D0) → Post-engraftment period

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