NEW DIRECTIONS IN APLASTIC ANEMIA: WHAT’S ON THE HORIZON?

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Aplastic Anemia is Bone Marrow Failure

- The bone marrow is the spongy stem cell tissue that produces the blood:
  - Red cells
  - White cells (neutrophils)
  - Platelets
- When all three cell lines are low → Pancytopenia

Classification of AA: Camitta Criteria

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TREATMENT LINGO
Stem Cell Transplant

Types of Transplant
- Depends on:
  - Stem cell source
  - Donor relationship to patient
  - Conditioning regimen

Hematopoietic stem cell (HSCT)
- Hematopoietic stem cells divide to form more blood-forming stem cells
- Or they mature into 1 of 3 types of blood cells—white or red blood cells and platelets
- THE GRAFT = source of stem cells
- Sources of stem cells
  - BMT: bone marrow transplant
  - PBSC: peripheral blood stem cell transplant
  - UC: umbilical cord transplant
- Cells from any of these sources can be used in transplants

Donors
- Allogeneic- patients receive stem cells from another person
  - Related
    - Full matched sibling
    - Half matched sibling
  - Unrelated
    - Mismatched
- Autologous- patients receive own stem cells—*not in AA*
- Syngeneic- patients receive stem cells from identical twin

Conditioning regimens
- Also called preparative regimens
  - Nonmyeloablative = “mini”
    - Standard of Care with matched siblings
    - Antithymocyte globulin (ATG) +/- cyclophosphamide
    - Fludarabine + Total body irradiation (TBI) + cyclophosphamide
    - Alemtuzumab (Campath) + TBI + cyclophosphamide
  - Myeloablative = “maxi”
    - Used infrequently
    - Facilitate engraftment
    - Infertility concerns

Graft versus Host Disease (GVHD)
- Transplanted immune cells from the donor attack the patient’s body cells
  - Acute (<100 days)
  - Chronic—can decrease long term survival
  - Can affect nearly any organ
    - SKIN
    - GUT
    - LIVER
    - Lungs
    - Eyes
    - Vagina
**HOW DO WE DECIDE?**

Allogeneic BMT for SAA
- Affected by
  1. Age of patient (recipient)
  2. Availability of donor
- These are the 2 most important prognostic factors for survival
- Children and adults approached differently in this context

**Young patients (<30-40 years Old) Severe Aplastic Anemia**

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<td>Hematopoietic Cell Transplant</td>
<td>Immunosuppressive Therapy</td>
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<td>Response</td>
<td>Relapse</td>
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<td>Alternative donor transplantation versus repeat immunosuppression</td>
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<td>Clinical follow up</td>
<td>Assessment of late effects</td>
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<td>No Response</td>
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**Bone marrow transplant**
- Children, adolescents and young adults (age of <30-40 years) with SAA who have an HLA-matched sibling donor should proceed directly to BMT as this is potentially curative
- Marked reduction in the risk of relapse
- Decreases risk for late clonal disorders such as MDS and PNH

➤Ask your doctor about typing ASAP

**HLA Typing** (Human leukocyte antigen)
- Method to determine how closely the tissues from one person match the tissues from another person
- Requires a blood test (or other body tissue) to do this
- “Blood type” is less important and different than HLA type
- Goal: for the 2 immune systems to NOT see each other as “foreign” and be less likely to attack each other
  - Siblings: 25% chance full match, 25% chance no match, 50% chance half match
  - Two unrelated people can be a good HLA match as well (“MUD”)
HLA Typing (continued)

- HLA matching is usually based on 8 or 10 HLA molecules (more is better match)
- HLA markers looked at for these minimum requirements are two A, two B, two C, and two DRB1 (DQ also done)

Questions you might be asked:
- What is the urgency? (APLASTIC ANEMIA)
- What is treatment plan?
- Search for an alternate donor if there is no family match?
- Insurance and contact information for patient/ potential donors is important

Older patients (>40 years Old) or No Suitable Donor

Severe Aplastic Anemia

- Immunosuppressive Therapy
  - Response
  - No Response
  - Clinical follow up
  - Alternative donor transplantation (or matched sibling) versus repeat immunosuppression
  - Assessment of late effects

Locasciulli A et al. Haematologica 2007;92:11-18

All outcomes improving with time

BMT compared to IST

- 10 year survival for BMT 73% and 68% for IST (data 1991-2002)
  - p=0.002
  - All outcomes improving with time

Langerak A et al. Haematologica 2007;92:11-18
ONWARD TO TRANSPLANT

What helps outcomes \(\rightarrow\) predictors of survival:

- Recipient age of less than 16 years
- Matched sibling donor
- Early BMT (time from diagnosis to BMT of less than 83 days)
- Using bone marrow source (over peripheral stem cells)
- Non-radiation conditioning regimen (ATG, Campath)

Locasciulli A et al. Haematologica 2007;92:11-18

Survival is better in children than adults

Locasciulli A et al. Haematologica 2007;92:11-18

Why we do not rush to BMT in older patients

Survival is less

GVHD is more

Sangiolo et al. BBMT 2010

Conditioning: ATG+CY

- Antithymocyte globulin (ATG)- added to prevent graft rejection, lower rates of cGVHD
  - Big part of immunosuppressive even if no BMT
- Cyclophosphamide- immunosuppressive but not marrow ablative
  - Cardiac toxicity
  - Hemorrhagic cystitis (bladder bleeding)
  - Alopecia (hair loss)
- Radiation has longer term toxicities and is probably not needed

Chalmelin et al., Blood 2009
Storb et al., BBMT 2001
Storb et al., Blood 1997
**Bone marrow source is better than Peripheral blood**

- **GVHD**
  - More GVHD if older and use PBSC

- **Overall survival**
  - Higher survival if younger and use bone marrow

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**HIGH DOSE CYCLOPHOSPHAMIDE**

*Another form of IST*

- High dose = 50mg/kg daily for 4 days (similar to conditioning regimen for BMT)
- 66 patients studied at Hopkins
  - 44 treatment naïve (Response: 31/44 = 71%)
  - 23 refractory to standard ATG/CSA
- Median follow-up 63 months
- Median time to response: 5 (IQR, 2-10) months
- Study at NIH stopped due to toxicity from HiCY
- Even moderate doses of CY may be too toxic from fungal infections

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**OLDER PATIENTS (>40 years OLD) or NO SUITABLE DONOR**

**Severe Aplastic Anemia**

- Immunosuppressive Therapy
  - Response
  - No Response
  - Alternative donor transplantation (or matched sibling)
  - Clinical follow up
  - Relapse

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**UNRELATED DONOR OR ALTERNATIVE DONOR BMT**

- The sooner, the better after relapse/ refractoriness noted
- Bone marrow still the best source
- Similar conditioning regimens
- GVHD currently TOO HIGH
- Often in setting of clinical trial (as results need improvement)

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**URD IN CHILDREN**

- 44 children in UK (40 s/p IST)
  - Fludarabine, CY, Alemtuzumab conditioning
  - Overall survival and failure free survival was 95%
**Adult URD**

- Survival now >75%
- Similar conditioning regimens- may add TBI

**Haploidentical transplants**

- Reserved for refractory SAA
- Should be done in a specialist center
- Usually performed in setting of clinic trial
- Similar results to matched sib BMT for leukemia
- ~Everyone has a donor
  - Including those with little chance of match in unrelated registries (e.g., ethnic minorities)
  - Average person in US has 4.5 HLA haploidentical donors

**Haplo transplants done**

- 12 patients done in Korea (3 were treatment naïve) using nonmyeloablative conditioning
  - All 12 alive and transfusion independent at 14 month
  - 3 patients had to have 2nd BMT due to failure to engraft
  - 2 had cGVHD grade 4
- 19 patients done in China for refractory disease using myeloablative conditioning
  - All engrafted
  - Half of patients had cGVHD grade 3-4
  - 65% alive at >2 years
  - Clinical trial open at Hopkins to use haplo donor in adults and children
    - 2 haplos alive and well >1 year without GVHD

**Umbilical Cord Transplants**

- Survival is still lower
- Conditioning regimens more varied
  - CY/Flu/ TBI
  - Melphalan/Flu/ TBI
- Japanese study
  - 12 adult patients
  - 11/12 engrafted
  - survival 10/12 median 36 mos
  - cGVHD still too high
- Clinical trials open in US

**GVHD**

- Treated with forms of immunosuppression
- Can decrease quality of life
- Can cause infections while immunosuppressed
- Can be fatal
- Increased risk with
  - Non matched sibling donor
  - Non bone marrow stem cell source

**GVHD (continued)**

- Prophylaxis- usually up to 1 year after BMT
  - Methotrexate
  - Cyclosporine
  - Mycophenolate mofetil
  - Tacrolimus/ sirolimus
  - Alemtuzumab pre transplant
  - Cyclophosphamide post transplant
- Treatment
  - Steroids
  - PUVA
  - Tacrolimus
GVHD results improving over time

- Descriptive analysis ~1700 patients with BMT 1995-2006 from CIBMTR
  - Varied regimens for prophylaxis
  - aGVHD 17% for MSD vs 44% URD
  - cGVHD at 1 year 20% for MSD vs 37% URD

- Study of patients by EBMT up to 2001
  - cGVHD (extensive) at 1 year 79% URD
  - GVHD prophylaxis with MTX alone increased this risk
  - Less with ATG/CY conditioning compared to conditioning with radiation

Ades et al. Blood. 2004 Apr 1;103(7):2490-7

Advantages of Post BMT CY for Haplos

- Similar results to matched sib BMT, but virtually everyone has a donor
- No delay to BMT - many patients cannot wait 3-4 months for MUD
- Excellent immune recovery - high Cy spares memory/quiescent lymphs
- Helpful for malignant diseases but especially suited for genetic and autoimmune disease =Aplastic Anemia

Post Transplant CY Hopkins 1960s-present

- CY post alloBMT prevented GVHD in mice (Santos/Owens – 1960s)
  - Only high doses (150-300 mg/kg) effective
  - Lower doses - little activity

- Standard Hopkins prophylaxis (1975-1984)
  - Low dose - 7.5 mg/kg/d x 4 (MTX schedule)
  - Randomized trial - less effective than CsA

- High dose Cy (200 mg/kg) prevents GVHD after haploBMT in mice (Luznik/Fuchs 2001)

Following chimerism is important

- Chimerism is what % of the donor the recipient becomes → goal 100% donor
- Can be checked in blood and marrow
- Progressive mixed chimeras are at increased risk of late graft rejection when immunosuppression is withdrawn
- Monitoring after transplant is important

Supported Care

- Central Venous Catheter
  - considered for all patients with AA, given the frequency of phlebotomy, transfusions, and administration of therapeutic medications (PICC, Hickman, Mediport)

- Blood transfusions
  - Irradiated – prevent transfusion associated GVHD
  - Leukofiltered – reduce viral infections and prevent alloimmunization

- Growth factors
  - May provide clinical benefit but do not induce disease remissions

- Infections
  - Granulocyte transfusions –controversial
  - Antibiotics = important

Important Details

Supportive Care

Quellen K et al. Haematologica 2009.
Late effects after BMT

- Overall less than ~10% in series from CIBMTR, Seattle, EBMT
- More if unrelated donor than matched sibling
- More if exposed to total body irradiation
- More if +GVHD

- Avascular necrosis (up to 6%) (also after IST)
  - Hip or other persistent joint pain should prompt imaging to evaluate for avascular necrosis
  - Osteopenia may be seen if high steroid use

- Cataracts (up to 5%)
  - Routine ophthalmology exams will pick up

- Growth disturbance (up to 7%)

- Low thyroid levels (up to 6%)
  - Checked with bloodwork
  - Replacement hormone can be given

- Secondary malignancy (up to 2%)
  - Solid tumors
  - Lymphomas

- Infertility (up to 10%)

Fertility Preservation

- Fear of infertility – not a reason to withhold HSCT

- Female and male survivors after HSCT demonstrate fertility
  - Usually after non-myeloablative conditioning with ATG/cyclophosphamide

- Temporary ovarian and testicular dysfunction is common after cyclophosphamide
  - Fertility can return over the longer term (most pregnancies 5-10y post BMT)

Future Directions

- More use of alternative donor transplants
  - Expand the available donor pool

- Additional research on best conditioning regimen to maximize engraftment

- Techniques to encourage rapid hematopoietic reconstitution
  - G mobilized marrow from donor

- Improvements in prophylaxis against GVHD

Active Research

- >100 open clinical trials on clinicaltrials.gov (as of 8/2013)
  - Encourage your doctor to feel comfortable looking for all possible treatment options for you

- Transplant trials
  - Haploidentical BMT trial at Hopkins
  - Fludarabine+cyclophosphamide+TBI with double umbilical cords

- Non transplant trials
  - Eltrombopag
  - Alemtuzumab

Eapen et al. BMJ 2000;111:754-760
Loren et al, BMJMT 2011;17:157-166
Konopacki et al. Haematologica 2012;97:710-716
Summary

- Efficient HLA typing is important
- Upfront therapy for SAA in young patient is matched sibling transplant with ATG/CY
- Older patients or those without donor do immunosuppression with ATG/CsA first
- Bone marrow source from donor is best
- Late effects are manageable
- Active research ongoing

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Our Patients