Allo-HCT in Bone Marrow Failure Syndromes

A/Prof Nada Hamad

BSc MSc Forensic (hons) MBBS (hons) FRACP FRCPA SpeCetClinRes (Oncology)

TCT, Clinical and Laboratory Haematologist SVH

ANZTCT President | NSW BMT Network Chair | ALLG TCT Chair

UNSW Medicine EDI Deputy Co-Chair | Lancet Haematology EDI Lead

Pronouns: She/Her/Hers

On Gadigal Land

SAA

- Long-term survival ≥90%:
  - 5-year OS has improved in consecutive HCT eras
    - 58% Pre 2000, to 73% in 2001–2010, and 94% in 2011–2018.
  - Better donor selection
  - A reduction in the incidence, severity, and mortality from aGVHD
  - A reduction in the incidence of graft rejection
  - Early HCT before the onset of severe infections
  - Avoidance of transfusions prior to HCT

Upfront allo-HCT Rationale

- Improved outcomes with HCT
- Risks of severe infections
- Risks of excessive blood product transfusions
- Late clonal disorders such as MDS/AML with IST

Evidence of Efficacy

- Patient selection in real life is different to trials

- Early outcomes may favour IST but HCT is curative
  - 2 meta-analyses (7955 and 302 pts) found OS ≥IST
    - Peinemann et al PLoS One 2011 and Peinemann et al Cochrane Database Syst Rev 2013
  - Innovations in HCT & IST make historical comparisons difficult

- Patient preferences need to be taken into account

Disease /Patient/Donor Factors

- SAA and vSAA have a higher risk of poor outcomes without HCT
- Outcomes historically been better in younger patients
  - But growing evidence good outcomes in older patients
  - OS as high as 85% in >50y
    - Sheth et al Blood Adv 2019
    - Rice et al BBMT 2019
- Comorbidities
  - Infections and/or renal, hepatic, or cardiac dysfunction may preclude HCT
- MRD>MUD
  - Closer HLA matching reduces the risks of graft failure and GVHD
  - Better MUD outcomes make this almost comparable option to MRD
    - Dufour et al Br J Haematol 2015 and Kennedy-Nasser et al BBMT 2006
  - MRD faster access

How to achieve the best outcomes: Pre HCT

- Eliminate other diagnoses eg MDS/Mineral def/Fanconi
- Confirm eligibility by assessing organ function
- Identify active or latent infections
- Transfusion risk reduction
  - ↓ transfusions to avoid RBC Ag sensitisation → graft failure
  - Leucodepleted/ irradiated products ↓ TA-GVHD or FNHTR
  - CMV negative recipients should receive CMV-negative blood products

How to achieve the best outcomes: HCT

- Optimal donor: MRD>MUD
  - Limited evidence with syngeneic, cord or haplo

- Stem Cell source: Aim is to minimise GVHD
  - Historically BM preferred but less and less practical
  - HCT in 1448 pts MRD/MUD 2005 and 2009 OS advantage with BM
    - Bacigalupo et all Haematologica 2015
  - No direct PB vs BM comparison

How to achieve the best outcomes: HCT

- MRD conditioning:
  - Most common Cy-ATG: Cy 50 mg/kg/day on d -5 to -2 ATG 5 mg/kg/d on d-4 to -2
    - Need accurate Cy dose due to cardiotoxicity
      - Aljurf et al BMT 2013
  - Older patients FC-ATG
    - Flu 30 mg/m2/d on d – 5 to -2; Cy 30 mg/kg on d -5 to-2; ATG 2.5 mg/kg on d -4 to-2
    - Similar results <40 vs >40 y: TRM (5.4% vs 11.1%, p = 0.19) [18] and OS ((93.7% vs 88.9%, p = 0.20)
      - Shin et al BMT 2016
  - Rabbit preferred over horse ATG ↓ rates of a+cGvHD
    - Kekre et al Haematologica 2017

- MUD Conditioning: various Cy ATG, FC-ATG-TBI, FCC
  - FC-ATG-TBI: addition of TBI 2 Gy
    - Anderlini et al Lancet Haem 2015
  - FCC: Campath 10 mg/kg on days -7 and -3
    - Avoids TBI and associated with mixed T-cell chimerism without relapse or graft failure
    - Marsh et al BMT 2014
    - Hamad et al BBMT 2014

Complications and Supportive care

- GVHD prophylaxis: MTX and CNI
  - CNI alone eg in FCC

- Graft failure 10-20%
  - Minimise transfusion pre HCT
  - ATG in addition to Cy +/-Fludarabine
  - Adequate cell dose: nucleated cells >3 × 10^8/kg or 2 × 10^6 CD34+ cells/kg
    - Pulsipher et al Pediatr Blood Cancer 2020

- Infection prophylaxis and treatment
  - Bacterial, Fungal, Viral
  - PTLD (single dose 200mg rituximab)
    - Peffault de Latour et al Blood 2018

- Transplant late effects including fertility

Fanconi Anaemia

- Rare
- Usually treated with supportive measures
  - androgens, and growth factors
- In severe BMF, MDS, or AML HCT OS 70-90%
  - Poorer outcomes in MDS/AML and older age (>10)
    - Peffault de Latour et al Blood 2013
- MRD>MUD
- Unique sensitivity to HCT conditioning agents
  - Evidence favours lower dose Cy (↓TRM)
    - Zanis-Neto et al BJH 2005
  - ATG associated with better outcomes (↓ GVHD ? ↑Graft failure)
  - Fludarabine associated with better outcomes (↓ graft failure, ↓ GVHD ↓ TRM and ↑OS)
    - Wagner et al Blood 2007

Summary

- HCT outcomes in BMF have shown significant improvement in survival
- Need to consider contemporary alternatives in non HCT treatments
- Patient, donor and stem cell source selection important
  - Haplo still experimental
- Conditioning regimen improvements with ATG/Campath and Fludarabine additions to Cyclophosphamide