Alternate donor stem cell transplantation for children with Fanconi anemia

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Background

- Recent MSK multi-institutional study using a radiation free approach in 45 patients
  - Bu/Flu/Cy40/ATG and T cell-depleted PBSC
- Results encouraging
  - Engraftment – 95%
  - GVHD – severe acute or extensive chronic – 0%
  - OS at 1 year – 79%
    - 91% if </+ 10 years of age and transplanted for BMF

Question

- Can conditioning intensity be further reduced particularly in lower-risk patients?
  - Potential concerns:
    - Short or long-term graft failure
    - Failure to eradicate pre-malignant clones
  - Potential advantages
    - Acute: decreased TRM, decreased need for narcotics, TPN
    - Long-term: decreased risk of secondary malignancies

Study Design

- Treatment determined by **risk stratification** :
  - **Stratum 1:** Reduced **cytoxan** dosing for patients with marrow failure
  - **Stratum 2:** Standard conditioning for malignant disease

Eligibility Criteria

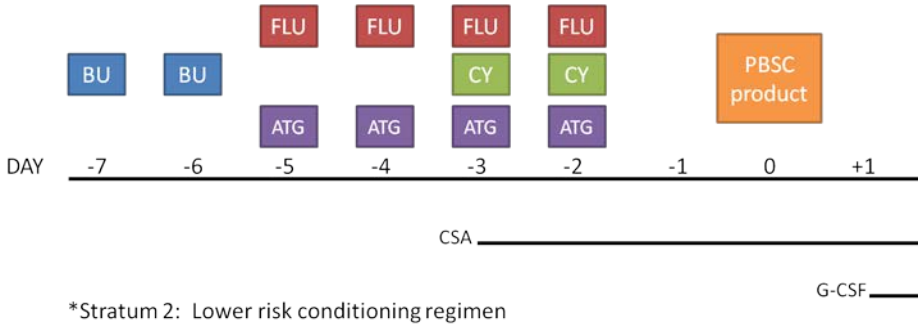
- Hematopoietic disease status:
  - Bone marrow failure
    - Platelet count < 20 x 10^9/L or platelet transfusion dependence
    - Hemoglobin < 8 gm/dL or red blood cell transfusion dependence
    - Absolute neutrophil count < 1000 x 10^6/L
  - Hematologic malignancy
    - Specific cytogenetic abnormalities (loss of 7p or gain of 3q)
    - Myelodysplastic syndrome
    - Acute myeloid leukemia

- Donors:
  - 8/8 or 7/8 HLA-matched unrelated volunteer donor
  - Haplo-identical donor

Treatment Plan

Stratum 1: Standard risk conditioning for participants with FA and BMF

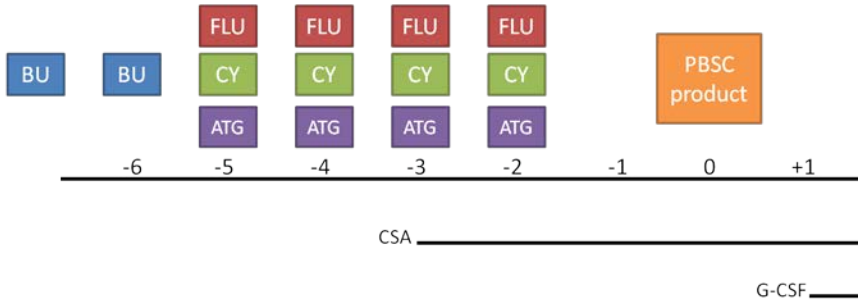
CY dose 20 mg/kg



*Stratum 2: Lower risk conditioning regimen

Stratum 2: High risk conditioning for participants with FA and progressive hematopoietic disease

CY dose 40 mg/kg



Stratum 1: Standard risk conditioning regimen

Primary endpoints

- **Incidence of primary neutrophil engraftment** by day +42

- **Day +100** survival

Secondary Endpoints

- Late graft failure/chimerism
- Acute Toxicity
  - PN/Narcotic use/Bacteremia
  - Viral reactivation/Infection
- Acute and chronic GVHD
- Relapse
- Overall Survival
- Immune reconstitution
- Secondary Malignancy
- Ovarian function

Statistical Considerations

- Anticipated **sample size** of 12 participants
- Total anticipated **study duration** of 7 years

Statistical Considerations

- Interim monitoring
  - Primary neutrophil engraftment
  - Survival to day +100 post-transplant

If 4 or more failures, stop for potential treatment modifications or study closure

Summary

- Recent collaborative work has demonstrated feasibility of reduced intensity radiation-free conditioning for FA patients with alternative donors
- Given excellent engraftment and superb OS in young patients with BMF we are investigating further reduction in alkylator therapy for this group
- Goal is to further decrease both short and long-term toxicity in this vulnerable population

Future directions

- Reduced reduced intensity (R^2)
  - Conditioning using immunosuppression alone
    - Fludarabine /campath
  - Pilot with 5 patients with DC
    - 100% survival with transfusion independence 5-34 months post-SCT
    - All 100% donor in myeloid cells, 3 patients > 2 years out are 100% donor in lymphoid as well
    - Minimal toxicity with viral reactivation being main AE
  - Use in FA patients
    - Could haven even greater impact on toxicity
    - Concern re graft failure, eradication of clonal hematopoiesis