Updates on alternative donor stem cell transplant (SCT) for Fanconi Anemia

A Radiation Free Approach

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Background

- Outcomes of stem cell transplantation (SCT) for bone marrow failure using matched family donors have improved dramatically over the past years
- Survival rates for children transplanted for bone marrow failure consistently exceed 80%
- Conditioning regimens employ cyclophosphamide +/- fludarabine and anti-thymocyte globulin (ATG) with no radiation

Background II

- By contrast transplants using unrelated donors for marrow failure have not been as successful
  - Increased rates of graft failure
  - Increased rates of GVHD
- Due to these concerns conditioning regimens have historically contained low dose total body irradiation (TBI)
- The chromosome fragility exhibited by FA patients makes them exquisitely sensitive to TBI and crosslinking agents used in conditioning

The problem with TBI and FA

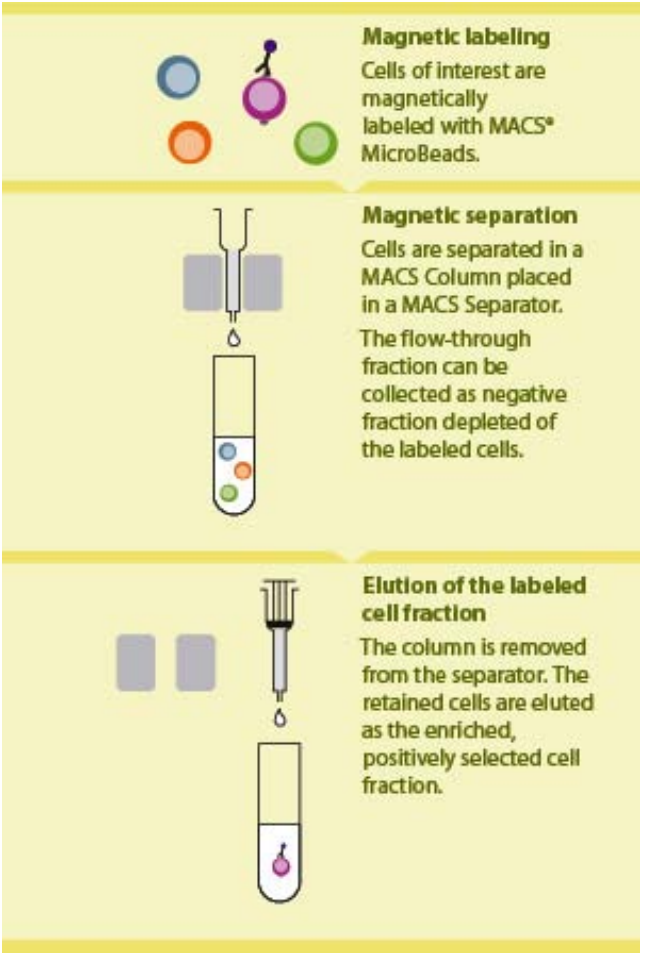
- Radiation and chronic GVHD are risk factors in non FA populations for squamous cell carcinoma (SCC) and solid tumors
- At baseline FA patients exhibit higher rates of cancer including > 200 times the expected rate for SCC of the head and neck (Rosenberg 2008)
- Following successful SCT solid tumors remain a significant obstacle to cure for patients with FA

Phase II protocol for SCT in FA

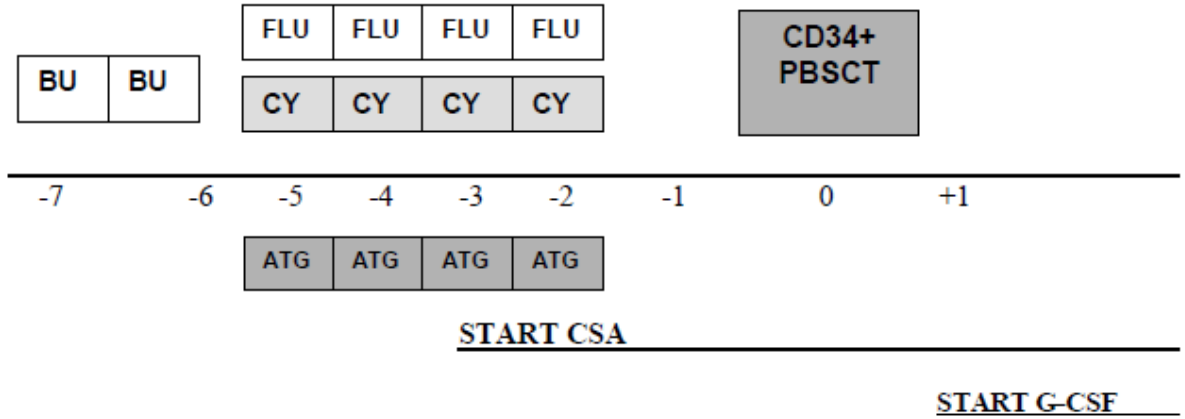
- The challenges of HSCT for FA using alternative donors are based on the need for a regimen
  - immunosuppressive enough to allow engraftment, with a low risk of rejection,
  - manipulates the graft to decrease the risk of GVHD
  - that does not give rise to excessive toxicity
- Dr. Boulad at MSKCC developed a radiation-free conditioning approach for SCT
  - Mismatched related donors
  - Matched unrelated donors

Protocol Overview

- Peripheral blood stem cell collection
- T cell depletion using CliniMacs column
- Radiation-free preparative regimen
- GVHD prophylaxis – cyclosporin
- Intensive infectious screening & prophylaxis



Preparative regimen



BU	Busulfan 0.8-1.0 mg/Kg/dose IV Q 12H	X 4 doses
FLU	Fludarabine 35 mg/m2/dose IV once daily	X 4 doses
CY	Cyclophosphamide 10 mg/Kg/dose IV once daily	X 4 doses
ATG	Anti-thymocyte globulin - Thymoglobulin 2.5 mg/Kg/dose IV daily	X 4 doses
CSA	Cyclosporine 2.5 mg/Kg/dose IV Q 8-12 H	
G-SCF	Filgrastim 5 mcg/Kg/dose IV Q 12H	

Patients

- 14 patients enrolled
  - Age 5-27 (median age 8)
- Indication for HSCT
  - Cytopenia/aplastic anemia – 11
  - Myelodysplastic syndrome – 3
- Donors
  - Parent – 4
  - Unrelated donor - 10

Results

- **11 of 14 children alive and disease free at 1-24 months (median 4 months) following SCT**
  - 100% engrafted
  - 1 case of veno-occlusive disease
  - Infections include CMV (2), C difficile (2), influenza A (1), HSV (2)
  - 3 fatalities: infection, pulmonary hypertension, multi-organ failure
- Multicenter trial: Children's Hospital Boston, Rockefeller University, Cincinnati Children's Hospital, Children's Hospital Wisconsin, Fred Hutchinson Cancer Center

Boston experience

2 patients

- Both had neutrophil engraftment on Day 16
- platelet engraftment on Day 14 and 16
- No acute GVHD

Conclusions

- Encouraging results for engraftment and survival using radiation-free regimen in an alternative donor setting
- Need longer follow-up to impact on chronic GVHD and secondary malignancy rates