Single Center Experience with Hematopoietic Cell Transplantation in Young Children with Chronic Granulomatous Disease

Jacqueline D. Squire, MD[1]; Shannon Sullivan, MD[2];Deepak Chellapandian, MD[3]; Jennifer W. Leiding, MD[1].

[1] University of South Florida, Allergy and Immunology; [2]University of South Florida, Pediatrics; [3]John Hopkin's All Children's Cancer and Blood Disorders Institute, Bone Marrow Transplant

Introduction

- Chronic granulomatous disease (CGD) is a primary immune deficiency caused by defects in the NADPH oxidase subunits.
- The only potentially curative option for CGD is hematopoietic cell transplant (HCT).
- Risks of HCT, including graft-versus-host disease (GvHD), complications of chemotherapy, and death, have often deterred physicians and patients from pursuing HCT early.[1]
- We reviewed the outcomes of HCT for CGD patients performed at our institution between August 2005 – October 2018.

Results

- Eight patients underwent HCT: 6 X-linked, 2 autosomal recessive
  - Median age of transplant: 2.2 y
- Pretransplant infectious complications:
  - Pneumonia in 3 patients (#3, 6, 8), lobectomy in 2 (#6, 8)
  - Lymphadenitis/skin abscesses in 3 (#1, 4, 5)
- Pretransplant inflammatory complications:
  - Lung granulomas in 2 patients (#1, 7)
  - Autoimmune hepatitis in 3 (#1, 2, 4)
  - Colitis in 2 (#2, 3)
- 3 received myeloablative conditioning, 5 received reduced intensity/toxicity conditioning
- All received 10/10 matched HCT, 4 related donors and 4 unrelated.
- Median neutrophil engraftment: 18.5 days
- All achieved primary engraftment, 1 had secondary graft failure at 1 yr s/p HCT
- 42% (3/7) maintain full donor chimerism, median follow-up 4.3 yr
- 42% (3/7) are mixed chimera, median follow-up 1.4 yr
- Overall survival: 87.5%

Table 1. Patient Characteristics and Outcomes of HCT

Patient	Sex	Gene	Age at diagnosis	Age at transplant	Donor	Pre-Conditioning	Outcome (length of follow-up)
1	M	*CYBB*	2.5 y	4.16 y	10/10 MUD	Bu/Flu/ATG (MAC)	Full donor chimerism (8.3 y)
2	F	*CYBA*	<1 mon	4.25 y	10/10 MRD	Mel/Flu/Thio/ATG (MAC)	Deceased, disseminated *Trichosporon* day +21
3	M	*CYBB*	2 mon	1.83 y	10/10 MRD	Bu/Cytoxan (MAC)	Full donor chimerism (4.3 y) Grade I GvHD, Pericarditis, Hypothyroidism
4	F	*CYBA*	4 mon	2.5 y	10/10 MRD	Mel/Flu/Campath (RIC)	Secondary graft failure at 1 y Granulomatous pneumonitis, uveitis, CGD-colitis
5	M	*CYBB*	3 mon	1.08 y	10/10 MUD	Bu/Flu/ATG (RTC)	Full donor chimerism (4 y) AIHA, ITP
6	M	*CYBB*	21 mon	3.75 y	10/10 MRD	Bu/Flu/ATG (RTC)	Mixed chimera, 93% (1.4 y)
7	M	*CYBB*	8 mon	1.58 y	10/10 MUD	Bu/Flu/ATG (RTC)	Mixed chimera, 60% (1.0 y)
8	M	*CYBB*	15 mon	1.66 y	10/10 MUD	Bu/Flu/ATG (RTC)	Mixed chimera, 70% (1.4 y) Grade I GvHD, EBV viremia

MUD = matched unrelated donor, MRD = matched related donor, Bu = busulfan, Flu = fludarabine, ATG = anti-thymocyte globulin, Mel = melphalan, Thio = thiotepa

Discussion

- Majority of published transplant cohorts involve older children, adolescent, and adult patients.[1,2,3]
- Our institution's experience demonstrates safety and efficacy with early HCT in patients with CGD.
- RTC using Bu/Flu/ATG appears to be well tolerated, even in very young children.

Contact:
Jennifer Leiding, MD: jleiding@health.usf.edu
Jacqueline Squire, MD: jsquire@health.usf.edu

References

1. Connelly JA, Marsh R, Parikh S, Talano J. Allogenic Hematopoietic Stem Cell Transplantation for Chronic Granulomatous Disease: Controversies and State of the Art. J Pediatric Infect Dis Soc. 2018 May; 7(Suppl 1): S31-S39.
2. Gungor T, Teira P, Slatter M, et al. Reduced-intensity conditioning and HLA-matched haemopoietic stem-cell transplantation in patients with chronic granulomatous disease: a prospective multicentre study. *Lancet*. 2014 Feb 1;383(9915):436-48.
3. Arnold DE, Seif AE, Jyonouchi S, et al. Allogeneic hematopoietic stem cell transplantation in adolescent patients with chronic granulomatous disease. *J Allergy Clin Immunol Pract.* 2019 Mar;7(3):1052-1054