Hemoglobinopathies, Primary Immune Deficiencies and Inborn Errors of Met - Basic Preclinical

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Cytomegalovirus Reactivation in Children with Hemoglobinopathies Who Undergo Hematopoietic Cell Transplantation with Distal Alemtuzumab


Introduction: Cytomegalovirus (CMV) viremia after allogeneic hematopoietic cell transplant (HCT) is associated with substantial morbidity. In vivo T cell depletion with alemtuzumab is a known risk factor for CMV reactivation. After observing very early CMV viremia in patients who received distal alemtuzumab in preparation for HCT for hemoglobinopathies, we implemented a quality improvement project to decrease the burden of CMV in this population.

Objective: To describe patterns of CMV reactivation before and after changing our CMV prophylaxis and surveillance strategies.

Methods: We reviewed medical records of children undergoing HCT for sickle cell disease (SCD) or beta thalassemia at Children’s Hospital of Philadelphia between 2007-2018, who received distal alemtuzumab containing conditioning regimens. Patients received alemtuzumab (48 mg, starting ~22 days before transplant) with fludarabine and melphalan. Beginning in February 2014, CMV seropositive (CMV+) patients received prophylaxis with valganciclovir from completion of alemtuzumab through day -1 and foscarnet starting on day 0, as well as weekly CMV surveillance beginning with alemtuzumab administration. Rates of CMV reactivation, as well as balancing metrics [time to engraftment and rate of acute kidney injury (AKI)] within 100 days post-HCT were evaluated before and after implementation of this preventive approach.

Results: Twenty-nine children were included in the analysis. The median age was 11.1 (range: 3.1 to 17.3) years at HCT, 22 (75.9%) patients had SCD and 8 (24.1%) had beta thalassemia. All patients received bone marrow grafts; 22 (75.9%) from HLA-identical siblings and 7 (24.1%) from unrelated donors. Prior to HCT, 13 patients were CMV+. Of those, 11 (84.6%) developed CMV reactivation (7/7 pre-intervention and 4/6 post-intervention). Time from alemtuzumab start to CMV reactivation, regardless of prophylactic strategy, is shown in Figure 1. CMV reactivation occurred at a median of 4 (range: -11 to +13) days after planned HCT. During the post-intervention period, CMV reactivation was identified in 2 patients prior to the start of the proximal cytotoxic phase of conditioning and HCT was delayed until viremia cleared. One CMV seronegative patient developed CMV viremia 47 days post-HCT. Median time to engraftment was similar before and after the intervention (12.5 versus 13 days), as was the proportion of patients with AKI (3/7 versus 1/6).

Conclusion: In this cohort, rates of CMV viremia were high and CMV reactivation often occurred very early in the transplant course. In two cases, CMV reactivation was identified prior to transplant day, necessitating a delay in HCT. Consideration should be given to implementing a program of screening or prophylaxis beginning as early as the start of alemtuzumab

Figure 1. Kaplan-Meier curve demonstrating time to CMV viremia after administration of distal alemtuzumab
administration in CMV+ patients. Further research is needed to determine the optimal prophylactic strategy.

**HEMOGLOBINOPATHIES, PRIMARY IMMUNE DEFICIENCIES AND INBORN ERRORS OF METABOLISM - CLINICAL**

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Assessment of Safety and Efficacy of PBSC Mobilization with G-CSF and CD34+ Enrichment and Pbmnc (CD3+) Addback in Familial Haploidentical (FHI) Adult Donors with Sickle Cell Disease Trait (SCDT) Prior to Allogeneic HSCT of High-Risk SCD Patients

**Bronwyn Gilliam Long**, Allyson Flower MD, Sandra Fabricatore MSN, RN, PN, Erin Morris RN, BSN, Harshini Mahanti BS, MSCR, Qiuhu Shi PhD, Carolyn A. Keever-Taylor PhD, Rona S. Weinberg PhD, Brenda Grossman MD, Julie-An M. Talano MD, Shalini Shenoy MD, Theodore B. Moore MD, Janet Ayello MS, MT(ASCP), Mildred Semidei-Pomales MS, Carmella van de Ven MA, Mitchell S. Cairo MD, Pediatrics, New York Medical College, Valhalla, NY; Epidemiology and Community Health, New York Medical College, Valhalla, NY; Medicine, Division of Hematology and Oncology, Medical College of Wisconsin, Milwaukee, WI; The New York Blood Center, New York, NY; Pathology & Immunology, Washington University, St. Louis, MO; Medical College of Wisconsin, Milwaukee, WI; Pediatrics, Washington University, St. Louis Children's Hospital, St. Louis, MO; Pediatric Hematology/Oncology, David Geffen School of Medicine at UCLA, Los Angeles, CA; New York Medical College, Valhalla, NY

**Background:** We and others have previously reported the safety of allogeneic stem cell transplantation in children with SCD without sibling HLA matched bone marrow donors who commonly have SCDT. The majority of the sibling donors donated bone marrow and received G-CSF mobilized PBSCs (Bhatia/Cairo et al, BMT 2014; Gluckman et al, Blood 2017). Furthermore, only 14-18% of siblings can serve as donors based on HLA match and presence of SCD (Mentzer, Am J Ped Hem/Onc 1994; Walters, BBMT 1996). Unrelated cord blood as a donor source for SCD patients was associated with unacceptable primary graft failure rates (Radhakrishnan/Cairo, BBMT 2013). MUD HSCT resulted in unacceptably high rates of GvHD (Shenoy et al, Blood 2016). Parental FHI SCDT PBSCs represent an alternative donor source. However, little is known about G-CSF PBSC mobilization in older donors with SCDT. GCSF mobilization of PBSC in homozygous SCD patients in the past has been reported to be associated with major toxicity and death (Adler et al, Blood 2001).

**Objective:** To determine if FHI PBSC mobilization in older adult donors with SCDS is safe and effective.

**Methods:** Eighteen FHI donors with SCDT received 15mg/kg/d GCSF divided BID x 4 days. PBSC leukapheresis on day 5, repeating qd until 10 x 10^6 CD34/kg and 2 x 10^5 CD3/kg (minimum) were cryopreserved. CD34+ enrichment utilized the Clinimacs® System (generously provided by Miltenyi), with 2 x 10^5 CD3/kg T-cell add-back before HSCT as we have previously described (Geyer/Cairo, BJH 2011). Donor chimerism assays for whole blood CD3, CD71, and CD56 were performed post-HSCT.

**Results:** Fifteen female/3 male FHI donors with SCDT were mobilized: mean age 41 yrs (30-55). The most common donor side effect was grade 1 bone pain (n = 11). Other side effects were grade 1 nausea/vomiting (n = 3), grade 1 headache (n = 2), grade 1 dizziness (n = 1), grade 1 fatigue (n = 2), grade 1 abdominal pain (n = 2), grade 3 bone pain (n = 1), and grade 3 thrombocytopenia (n = 1). The mean ± SEM CD34 count was 12.9 ± 0.8 x 10^6/kg recipient wt with the mean ± SEM yield 533.69 ± 48.9 x 10^6. Mean ± SD log T-cell (CD3) depletion was 4.84 ± 0.58 (Fig. 1). 100% of patients achieved neutrophil engraftment at a median of 9 days (range 6-13), and 92.1% of patients achieved platelet engraftment at a median of 19 days (range 8-90) (Fig 2A/2B, respectively). Mean ± SEM Blood and CD71+ (RBC) donor chimerism was 97.1 ± 1.4 and 96.4 ± 2.0%, respectively.

**Conclusion:** These data suggest that adult FHI stem cell donors with SCD undergoing GCSF mobilization for PBSC collection is safe and well-tolerated with only minor temporary adverse events. PBSC collection and CD34 enrichment was effective and resulted in successful SCDF recipient engraftment and long-term donor chimerism. Further studies are needed to evaluate the long-term outcome of high-risk SCD patients undergoing FHI AlloHSCT R01FD004090.

**Figure 1.** FHI Donor SCDS Donor Characteristics.

**Figure 2.** Probability of Neutrophil and Platelet Engraftment/Day.

Augmenting Non-Myeloablative BMT with Ptcy Using Thiotepa or 400 Cgy TBI Improves Engraftment in Patients with Transfusion Dependent Thalassemia: Results of a Haploidentical Transplant Consortium for Hemoglobinopathies (ICHII)

**Josu de la Fuente PhD, FRCP, MRCPCH, FRCPath**, Rabi Hanna MD, Christopher Gamper MD, PhD, Heather J. Symons MD, MHS, Leena Karnik MBBS, Dilan Anil Patel MD, James A. Connelly MD, Carrie L. Kitko MD, Adetola A. Kassim MD, MS, Kenneth R. Cooke MD, 1Department of Paediatrics, Imperial College London, London, United Kingdom; 2Department of Pediatric Hematology Oncology and Bone Marrow Transplantation, Cleveland Clinic Children's Hospital, Cleveland, OH; 3Pediatric Oncology, Johns Hopkins University School of Medicine, Baltimore, MD; 4Pediatric Oncology, The Johns Hopkins University School of Medicine, Baltimore, MD; 5Department of Paediatrics, St. Mary’s Hospital, Imperial College, London, United Kingdom; 6Hematology/Oncology, Vanderbilt University School of Medicine, Nashville, TN; 7Pediatric Blood and Marrow Transplant Program, University of Michigan, Ann Arbor, MI; 8Pediatric Blood