A protocol for matched unrelated donor hematopoietic stem cell transplantations for severe combined immunodeficiency

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ABSTRACT

Hematopoietic stem cell transplantation using HLA-mismatched related donors for the treatment of severe combined immunodeficiency has led to disappointing outcomes at our institution. This created an impetus to consider other donor sources when an HLA-matched related donor was not available. In 1988, a new protocol using HLA-matched unrelated donors was developed at our institution and continues to be used to date. This has contributed to improved outcomes and change in practice for patients with severe combined immunodeficiency.

Statement of novelty: This report describes in detail the protocol for hematopoietic stem cell transplantations using HLA-matched unrelated donors for patients with severe combined immunodeficiency at our institution. This protocol is published for those centres wishing for guidance in setting up procedures for hematopoietic stem cell transplantation.

Until 1987, the experience at the Hospital for Sick Children, Toronto, Ontario, with hematopoietic stem cell transplantation (HSCT) using HLA-mismatched donors for the treatment of severe combined immunodeficiency (SCID) was disappointing. Various methods of T-cell depletion of parental HLA-mismatched related donors (MMRD) HSCT had been used with no significant difference in outcomes. The majority of patients who had received HSCT using MMRD-depleted marrow at our institution prior to 1987 died of infections, graft versus host disease (GvHD), or graft loss. Those who survived experienced various degrees of acute and chronic GvHD as well as long-term autoimmune manifestations. Engraftment of lymphocytes was slow and late loss of graft was seen. Large European studies reported approximately 50% survival rate for mismatch donor transplants (Antoine et al. 2003). However, careful analysis of outcomes according to HLA matching showed a survival rate of 25%–30% for true half-matched donor transplants (Caillat-Zucman et al. 2004), which are very similar to the results obtained at our institution.

Despite these discouraging results, many centres worldwide adhered to this procedure for 2 more decades. In 1988, with the establishment of the early bone marrow donor registries, Dr. Chaim Roifman pioneered the use of matched unrelated donors (MUD) instead of depleted nonmatched related donors for SCID and other immune disorders. A similar protocol was simultaneously developed in Minnesota by Drs. Alexandra Filipovitch and Ralph Shapiro (Filipovich et al. 1992). With little historic evidence to support this approach, the protocol was approved at The Hospital for Sick Children and the first patient was enrolled in December 1989.

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Table 1: **HSCT protocol for patients with SCID using Busulfan and Cyclophosphamide**

Day –10	**Admit under reverse isolation (Reid and Courtney 2015)**
	Standing orders
	Irradiate all blood products and use CMV negative blood products
	Daily weight
	Bacti-stat bath daily
	Transfuse to keep hemoglobin > 70 g/L, platelets > 20 × 10^9/L
	Discontinue breast feeding or irradiate breast milk
	Standing bloodwork orders
	Send blood to Molecular Genetics lab for pre-HSCT recipient sample for donor chimerism
	CBC, Na, K, Ca, P, Mg, glucose, urea, creatinine, ALT, AST, GGT, conjugated bilirubin and unconjugated bilirubin daily
	Differential qMonday, Wednesday, Friday
	INR, PTT, NH_3, amylase, total protein, albumin, IgG level qMonday
	Urine total protein and albumin/creatinine ratio qWednesday if no hematuria
	Lipid levels twice per week while on TPN
	CMV, EBV by PCR, quantitative EBV by PCR, adenovirus by PCR qMonday
	Standing medication orders
	IVIG (0.6 g/kg/dose) IV over 2 h, once weekly if CMV positive or if IgG <6 g/L
	Sodium bicarbonate mouthwash 5 mL apply with cloth/toothbrush to teeth and gums QID for mouth care
	Eucerin® cream apply to skin daily after bath and PRN
	Discontinue previous cotrimoxazole order
	Cotrimoxazole (5 mg TMP/kg/dose) PO daily × 3 days
	Consider amphotericin for treatment and possibly prophylaxis of fungal infection until Day 0
	IV fluids at twice maintenance (125 mL/m^2/hour) + emesis – keep urine output at 3 mL/kg/h
	Phenytoin Protocol
	Start IV Phenytoin load (20 mg/kg/dose) **IV** and then 8 h later start maintenance Phenytoin (see guidelines at end of table) **PO** q8h and continue PO Phenytoin for 24 h after the last dose of Busulfan
Day –9	Consider Ganciclovir (5 mg/kg/dose) IV BID for CMV positive recipient
	Start Acyclovir (250 mg/m^2/dose) IV q8h for HSV prophylaxis (if not receiving Ganciclovir)
	Start Ondansetron (5 mg/m^2/dose, max 8 mg/dose) IV q12h (until Day –6)
	Start Dexamethasone 2 mg IV q12h if ≤0.6 m^2 or 4mg IV q12h if > 0.6 m^2 × 8 doses
	Start Busulfan (day # 1) (see guidelines at end of table) IV over 120 minutes in (0.5 mg/mL) Normal Saline q6h starting at 03:00
	Busulfan levels at 4, 5, and 6 h after the start of the Busulfan infusion
	Continue Phenytoin
Day –8	Continue Busulfan (day # 2, dose based on Busulfan levels and calculate area under the curve)
	Phenytoin level Continue Phenytoin
Day –7	Continue Busulfan (day # 3)
	Continue Phenytoin
Day –6	Continue Busulfan (day # 4)
	Continue Phenytoin
Day –5	Discontinue Busulfan
	Change frequency of Ondansetron (5 mg/m^2/dose, max 8 mg/dose) IV to **q8h**
	Change dose of Dexamethasone to (6 mg/m^2) IV q6h
	Start Lorazepam (0.025 mg/kg/dose) IV q6h prn nausea/vomiting
	Start Cyclophosphamide (dose #1) (50 mg/kg/dose) IV in (use 100 mL for dose ≤1500 mg; use 250 mL for dose >1500 mg) normal saline over 60 min
	Start Mesna (10 mg/kg/dose) IV 15 min pre-Cyclophosphamide and q4h × 6 post-Cyclophosphamide – run over 15 min
	Continue Phenytoin

Continues

Table 1: Continued

Day –4	Discontinue Phenytoin		
	Cotrimoxazole (5 mg TMP/kg/dose) TMP PO daily × 3 days		
	Continue Cyclophosphamide (dose # 2) as described above		
	Continue Mesna as described above		
Day –3	Start Cyclosporine A (1.5 mg/kg/dose) IV q12h over 2h		
	STANDING ORDER: draw pre-Cyclosporine A level qMonday, Wednesday, Friday (target level: 150–200 mcg/L)		
	Continue Cyclophosphamide (dose # 3) as described above		
	Continue Mesna as described above		
Day –2	Continue Cyclophosphamide (dose # 4) as described above		
	Continue Mesna as described above		
Day –1	IV fluids at 1.5× maintenance		
	Discontinue Cyclophosphamide		
	Discontinue Mesna		
	Discontinue Ganciclovir if used		
Day 0	Reassess antiemetics		
	IV fluids at maintenance		
	Discontinue Dexamethasone if not already discontinued		
	Start Methylprednisolone (1 mg/kg/dose) IV q12h		
	Start Fluconazole (5 mg/kg/dose, max 400 mg/dose) PO/IV daily		
	Start Pentamidine (4 mg/kg/dose) IV q2weeks until Cotrimoxazole restarts		
	Hematopoietic progenitor cell infusion orders IV hydration (125 mL/m^2/h) for 2h pre- and 4h post-HPC infusion, then resume previous hydration order Ensure anaphylaxis kit available and MD on site Continuous ECG monitoring and Oxygen saturation monitoring Vital signs (temperature, HR, RR, BP) q15min Diphenhydramine (1 mg/kg/dose) IV, give once 30 minutes prior to HPC infusion Acetaminophen (10 mg/kg/dose) PO, give once 30 minutes prior to HPC infusion Meperidine (1 mg/kg/dose) IV q2h PRN rigors during HPC infusion Infuse HPC 3-5 × 10^8 TNC/kg (reduce volume for small recipients, RBC reduce for ABO incompatibility)		
	Once neutrophil engraftment occurs (ANC ≥0.5 × 10^9/L × 3 consecutive days)**:**		
	Discontinue Fluconazole		
	Discontinue Acyclovir on Day +28 or discharge, whichever comes sooner		
	Start Cotrimoxazole (5mg/kg/day) TMP PO daily 3 days per week when ANC >0.5 × 10^9/L and platelets >50 × 10^9/L Or continue Pentamidine (4mg/kg/dose) IV q2weeks if Cotrimoxazole delayed Or Dapsone (2 mg/kg/dose) PO daily		
	Restart Ganciclovir (5 mg/kg/dose) IV daily for CMV positive recipient or CMV positive donor		
Phenytoin Dosing			
Loading dose	Do NOT use suspension for loading dose 1. Capsules or Chewtabs: 6.6 mg/kg PO q3h × 3 doses or 2. Intravenous: 20 mg/kg IV over 1h		
Maintenance dosing, to start 8 hours after loading dose			
	Age	**Dose (mg/kg/day)**	**Dosing interval**
	≤3 years	8–10	q8h
	4–6 years	7.5–9	q8h
	7–9 years	7–8	q8h
	10–16 years	6–7	q8 or 12 hours

Continues

Table 1: Continued

Phenytoin Dose adjustment	**Level**	**Change**
	<20 micromol/L	Reload (10–20 mg/kg) IV and change maintenance to IV
	20–40 micromol/L	Reload (10 mg/kg) and increase maintenance by 1 mg/kg/day
	40–80 micromol/L	No change
	>80 micromol/L	Hold/reduce maintenance dose
Busulfan dosing – area under curve target is 900–1500 μM min	**Weight (kg)**	**Busulfan Dose (mg/kg/dose)**
	<9	1.0
	9 to <16	1.2
	16 to <23	1.1
	23 to 34	0.95
	>34	0.8

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; Ca, calcium; CBC, complete blood counts; CMV, cytomegalovirus; EBV, Epstein-Barr virus; GGT, gamma-glutamyl transferase; INR, international normalized ratio; IVIG, intravenous immune globulin; K, potassium; Mg, magnesium; Na, sodium; NH_3, ammonia; P, phosphate; PCR, polymerase chain reaction; PTT, partial thromboplastin time; TMP, trimethoprim; TPN, total parenteral nutrition.

He received his MUD HSCT in April 1990 while admitted to the intensive care unit. He engrafted promptly and was off GvHD prophylaxis and completely immune reconstituted by 8 months of age. The subsequent cases to receive MUD HSCT were a stark contrast to the previous experience with MMRD HSCT as all patients were discharged from the hospital within 3–6 months, engraftment was rapid, and complete and durable and immune reconstitution was maintained for at least more than 2 decades. Complications were limited to GvHD. In the following years, the results remained excellent as initially reported (Dalal et al. 2000). The key to the durability of this modality of HSCT was the consistency in outcomes obtained in centres around the world (Grunebaum et al. 2006). This was initially achieved thanks to the work of an exceptionally dedicated group of individuals including Brenda Reid, RN, and clinical and research fellows Drs. David Hummel, Stephen Feanny, Naftaly Meydan, Ilan Dalal, and Shai Cohen.

Currently in its third decade, this protocol (see Table 1) has undergone further improvements and expansions with the help of the highly talented members of the Division of Immunology/Allergy at our institution. Former fellows and current staff, Drs. Adelle Atkinson, Eyal Grunebaum, and Julia Upton, contributed immensely with pre-transplant preparation and counselling with families, establishing an Immunology Transplant Board, and formulating a defined tapering regimen for immunosuppression post-transplant. Many of these activities were supported by an extremely competent group of clinical assistants who have contributed to the care of our patients since 2002 including Drs. Sean Bulley, Karen Mandel, Maria Triassi-Asper, Raz Somech, Amit Nahum, Julia Upton, Fotini Kavadas, and this author.

Although the core of the protocol, such as chemotherapy conditioning and GvHD prophylaxis regimens, remained unchanged, all of the additions and improvements culminated in this solid and balanced treatment guidance for patients who require HSCT and have no HLA-matched related donor. This protocol helped change treatment practice for SCID in many jurisdictions worldwide including recent recommendations by the collaborative group (European Group for Blood and Marrow Transplantation 2011).

We have not yet reached a full cure for all patients receiving MUD HSCT and there remain challenges to overcome. It is therefore important to view this protocol as a dynamic work in progress with possible modifications according to new evidence.

This protocol is published for the benefit of centres that need guidance in setting up HSCT procedures. Because of a growing number of requests for it, we believe that wide distribution through publication in LymphoSign Journal will meet that need.

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