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Umbilical Cord Blood Transplant for Children with Myeloid Hematological Malignancies (UCAML)

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Umbilical Cord Blood Transplant for Children with Myeloid Hematological Malignancies (UCAML)

CHECKLIST FOR PATIENT ELIGIBILITY AND NECESSARY INFORMATION

Patient ID _____
Patient Name_____

YES	NO	VALUE/DATE	
Any "NO" answers will make a patient ineligible for study participation:			
____	____	_____	Patients with a myeloid hematologic malignancy (acute myelogenous leukemias, secondary myelogenous leukemia or myelodysplastic syndrome) unlikely to be cure by standard chemotherapy. This includes patients who have relapsed after standard chemotherapy treatments and patients in first remission with unfavorable prognostics features.
____	____	_____	UCB units identified as the HSC source must be HLA matched at 5-6 HLA- A and B (at low to intermediate resolution) and DRB1 (at high resolution).
____	____	_____	Total cryopreserved HSC graft cell dose must be $\geq 4 \times 10^7$ nucleated cells per kilogram recipient body weight.
____	____	_____	Lansky/Karnofsky scores $\geq$ 60
____	____	_____	Written informed consent and/or signed assent line from patient, parent or guardian.
____	____	_____	Negative Pregnancy Test, if applicable
Any "YES" answers will make a patient ineligible for study participation:			
_____	____	_____	Severe intercurrent infection (see Section 3.2.1)
_____	_____	_____	Severe renal disease (Creatinine > 3X normal for age)
____	_____	_____	Severe hepatic disease (direct bilirubin > 3mg/dl, or SGOT > 500)
_____	_____	_____	Patient has DLCO < 50% predicted or FEV1 < 50% of predicted, if applicable
_____	_____	_____	Patients with symptomatic cardiac failure unrelieved by medical therapy or evidence of significant cardiac dysfunction by echocardiogram (shortening fraction <20%).
____	____	_____	HIV Positive

Patient/Guardian able to give informed consent: _____
Signature of MD: _____Date:_____
To check eligibility of a patient, call Dr. Martinez 832-824-4692.

1.0 OBJECTIVES

1.1 Primary Objective

1.1.1 To determine the safety and overall survival at 100 days, 1 year, and 3 years after umbilical cord blood transplant in pediatric patients with myeloid hematological malignancies.

1.2 Secondary Objectives

1.2.1 To evaluate donor engraftment at 100 days, 6, 9, 12, 24 and 36 months after transplant.

1.2.2 To determine neutrophil recovery at Day 42 and platelet recovery at Day 180.

1.2.3 To estimate the risk of severe grade III-IV acute GvHD at Day 100.

1.2.4 To estimate the risk of chronic GvHD at 1 year.

1.2.5 To assess leukemia free survival at 1 and 3 years.

1.2.6 To assess relapse rate at 1 and 3 years after transplant.

1.3 Exploratory Objective

1.3.1 To evaluate T/B/NK cell recovery and function at day 100, 6, 9, 12, 24 and 36 months after transplant.

2.0 BACKGROUND AND RATIONALE

2.1 Introduction

Umbilical cord blood (UCB) is a readily available alternative source of HSCs that is capable of reconstituting hematopoiesis after myeloablative therapy. A recent survey by the Institute of Medicine found that more than 180,000 UCB units have been banked and more than 6,000 unrelated donor UCB transplantations have been performed [1-8]. In recent years, use of umbilical cord blood as an alternative source of transplantable haemopoietic stem cells has increased substantially, extending the availability of this treatment, especially for children.

2.2 Background of Hematological Malignancies and Cord Blood Transplantation

Despite major advances in curing children with leukemias over the last 30 years, approximately 20% of patients relapse and are candidates for transplantation [1]. Many of these patients will not be able to identify a matched related or unrelated bone marrow donor in a timely fashion. Transplantation of bone marrow from an unrelated adult volunteer donor however is limited by HLA-matching requirements, high risk of graft-versus-host disease (GvHD), opportunistic infections, and donor availability. In recent years, use of umbilical cord blood as an alternative source of transplantable haemopoietic stem cells has increased substantially, extending the availability of this treatment, especially for children. Although time to engraftment is slower, most reports show a lower risk of severe GvHD after transplantation of unrelated-donor umbilical cord blood than of unrelated-donor bone marrow, despite the frequent use of HLA-mismatched graft for transplantation of umbilical cord blood [9-19].

Recent results of COBLT, a multi-institutional, prospective NIH-sponsored trial of unrelated donor UCB transplantation, have further advanced the field of UCB transplantation. In this Phase II study, 191 pediatric patients diagnosed with a

hematologic malignancy [(median age = 7.7 years) (range: 1-18)]; [(median weight = 25.9 kg) (range: 7.5 – 118.4 kg)] were transplanted with one UCB unit. All patients received total body irradiation (TBI), cyclophosphamide and antithymocyte globulin (ATG) for pre-transplant conditioning, and post-transplant cyclosporine and methylprednisone for GvHD prophylaxis. The median cell dose delivered as measured by the pre-cryopreservation cell count was 5.2 x 10^7 cells/kg and 1.5 x 10^5 CD34 cells/kg. Donor selection was based on low resolution DNA-based HLA typing at Class IA and B, and high resolution DNA-based typing at Class II DRB1. The cumulative incidence of neutrophil engraftment, defined as achieving an ANC of 500/mcL by Day +42 with > 90% donor chimerism, was 75% (95% confidence interval [CI] 69-81%). The cumulative incidence of platelet engraftment, defined as maintaining a platelet count of > 50 x 10^9/L without transfusion support by Day 180 was 50% (95% CI 42-59%). The cumulative incidence of acute grades III/IV GvHD at Day +100 was 19% (95% CI 12-24%). The incidence of chronic GvHD at 1 year was 20% (95% CI 15- 26%) with 70% of the chronic GvHD classified as limited disease. In multivariate analysis, HLA matching was associated with the incidence of GvHD (P = 0.007). Most of the children enrolled on this study had high risk (CR1 with high risk features, CR2-3, active disease) hematologic malignancies. Their cumulative incidence of relapse at one year was 19% (95% CI 14-25%). Overall 95/191 patients died on study, with 41% of deaths from relapse, 19% from graft failure, and 18% from GvHD (50% of those dying from GvHD had infection as a secondary cause of death) [20].

2.3 Justification for Umbilical Cord Blood Transplantation

The major limiting step to HSCT in hematologic diseases is the availability of a suitable matched stem cell source. It is well known that delaying a HSCT in patients with malignacies increases the risk of infections, organ damage, and progression of the disease. Recent reports demonstrate the successful use of unrelated cord blood transplantation for the treatment of malignant and non-malignant diseases. Umbilical cord blood transplantation has extended the availabitliy of allogeneic hematopoietic SCT to patients who would otherwise not be eligible for this curative approach. Currently, large inventories of UCB units are available in public banks for transplantation in those lacking bone marrow donors. In some experienced centers, unrelated umbilical cord blood (UCB) has become an acceptable and sometimes a preferred stem cell source because of its availability and lower incidence of graft-vs-host-disease (GvHD). In 2003, Michel et al. [29], on behalf of Eurocord, analyzed 95 children (16 years old or less) who underwent unrelated CBT for AML (1994-2002). In all, 20 were transplanted in CR1, 47 in CR2, 5 in CR3 and 23 were not in remission. Poor prognosis cytogenetic abnormalities were identified in 29 of 81 available cases (36%). TBI was given in 44 children and BU ot 47. CSA and steroid were used to prevent GvHD in 63 cases. The number of HLA disparities range from 0-3/6. The median number of infused nucleated cells was 4.4 x 10^7/kg. Cumulative incidence of neutrophil recovery at Day 60 was 78%, 100 day acute GvHD incidence was 35% and 100 day TRM was 20%. The 2 year cumulative incidence for relapse was 29%. This study confirmed that UCB is an adequate alternative of a stem cell source in patients with AML.

2.4 Major Problems after Umbilical Cord Blood Transplant

The disadvantages of UCSCT include non-availability of the donor for booster stem cell infusion, lack of viral-specific cytotoxic T cells, slower engraftment and small stem cell dose. Infection-related treatment-related mortality is still of concern after UCBT; rates of haemopoietic recovery are slower after UCBT, therefore infectious complications including viral infections or reactivations occur frequently. The two major causes of death after umbilical cord blood transplantation for congenital disorders reported in the literature are graft failure (20%) and infection (15%) [11-21].

2.5 Protocol Proposal

In our study, we will use busulfan and cyclophosphamide (BuCy) backbone with the addition of fludarabine as the preparative SCT regimen. As an attempt to improve engraftment rate and reduce infections, two major causese of death reported on the COBLT study, we are going to incorporate fludarabine in the conditioning regimen. Purine-analogs, in particular fludarabine, have emerged as powerful immunosuppressive agents with minimal systemic toxicities. Fludarabine-based preparative regimens have been shown to allow alloengraftment in the related and unrelated donor setting with acceptable systemic toxicity in patients with a variety of hematologic malignancies.

The use of a BuCy backbone has been widely used and comparable to total body irradiation and cyclophosphamide (Cy/TBI) regimen. Although Cy/TBI was found to be significantly better in a randomized French study of adult patients, these results were not confirmed in a similar French pediatric study comparing Bu/Cy to Cy/TBI [24, 25]. Children with AML treated with Bu/Cy had EFS of 80%, compared to 42% following TBI. Finally, a comparison of the two regimens in patients with AML from the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT) could find no difference in leukemia-free survival in 237 patients treated with Bu/Cy versus 237 patients treated with Cy/TBI [26]. Avoiding irradiation in pediatric patients is desirable to minimize growth retardation and intellectual deficits. An initial study by Wingard et al. showed that growth impairment may be similar with the two cytoreductive regimens [27]. Two subsequent more comprehensive analyses demonstrated that non-TBI containing regimens do not cause growth failure following SCT [28]. A review of the relevant literature reveals that Bu/Cy regimens are as effective as TBI regimens, with fewer late effects, and will therefore be used as the standard backbone cytoreductive regimen for SCT patients in this protocol.

Encouraging data on adding fludarabine to the SCT regimen have been reported. A fludarabine-based, conditioning regimen, with adequate immunosuppressive activity could conceivably allow engraftment of stem cells from alternative donors in hematologic malignancies patients with acceptable engraftment rates and low transplant-related mortality. Regimen-related toxicity is believed to be a major contributing factor to GvHD. Therefore this approach may also lead to reduced GvHD, as some investigators have suggested [22, 23].

In our study, as an attempt to decrease the rate of viral infection and reactivation, we will avoid ATG (Thymoglobulin) / Campath (anti-CD52), and instead administer

MMF. The addition fludarabine should compensate any increase risk of graft failure with the removal of the ATG/Campath. We anticipate that the removal of ATG/Campath will facilitate immune reconstitution more efficiently after receiving a UCBT.

3.0 ELIGIBILITY

3.1 Inclusion Criteria

3.1.1 Patients with a myeloid hematologic malignancy (acute myelogenous leukemia, secondary myelogenous leukemia or myelodysplastic syndrome) unlikely to be cure by standard chemotherapy. This includes patients who have relapsed after standard chemotherapy treatments, and patients in first remission with unfavorable prognostics features.

3.1.2 Related or unrelated umbilical cord blood unit with 0-1 antigen mismatch at HLA-A and B (at low resolution) and DRB1 (at high resolution) with a total nucleated cell dose of $\geq 4 \times 10^7$/kg.

3.1.3 Lansky/Karnofsky scores ≥ 60.

3.1.4 Written informed consent and/or signed assent line from patient, parent or guardian.

3.1.5 Negative pregnancy test, if applicable.

3.2 Exclusion Criteria

3.2.1 Patients with uncontrolled infections. For bacterial infections, patients must be receiving definitive therapy and have no signs of progressing infection for 72 hours prior to enrollment. For fungal infections, patients must be receiving definitive systemic antifungal therapy and have no signs of progressing infection for 1 week prior to enrollment. Progressing infection is defined as hemodynamic instability attributable to sepsis or new symptoms, worsening physical signs or radiographic findings attributable to infection. Persisting fever without other signs or symptoms will not be interpreted as progressing infection.

3.2.2 Severe renal disease (creatinine > 3X normal for age)

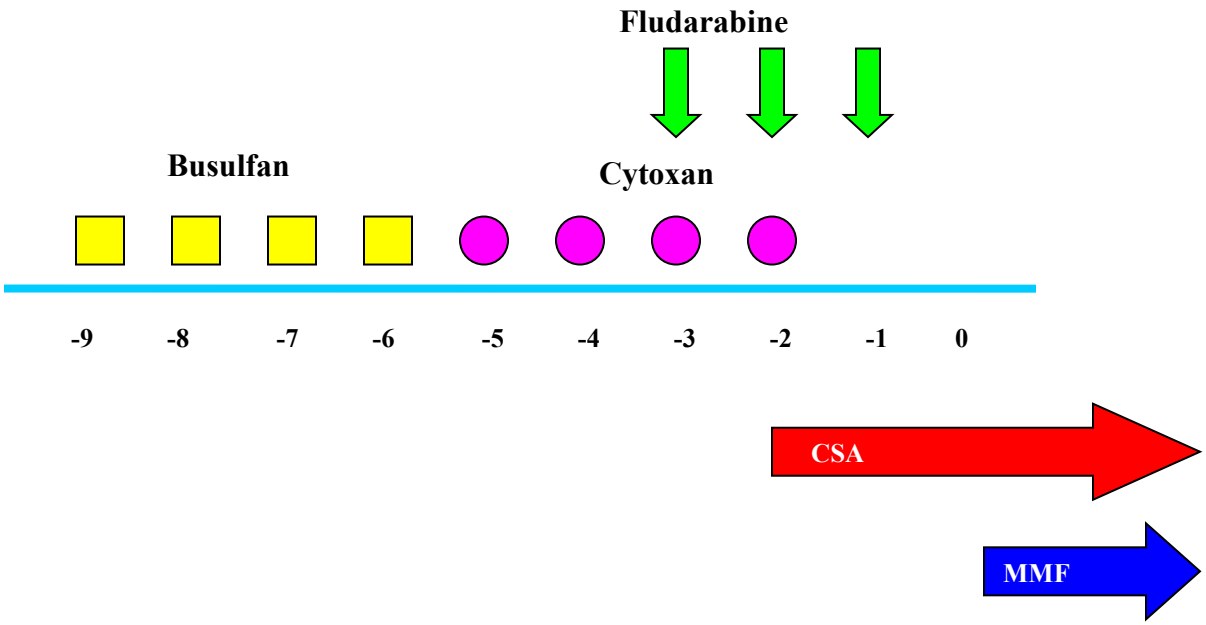
3.2.3 Severe hepatic disease (direct bilirubin > 3 mg/dL or SGOT > 500)

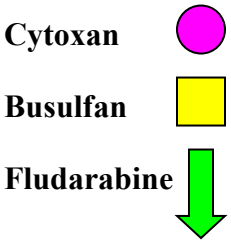
3.2.4 Patient has DLCO < 50% predicted or FEV1 < 50% of predicted, if applicable.

3.2.5 Patients with symptomatic cardiac failure unrelieved by medical therapy or evidence of significant cardiac dysfunction by echocardiogram (shortening fraction < 20%).

3.2.6 HIV positive.

4.0 Preparative Therapy / Immunosuppressive Therapy





Day	Agent	
-9	Busulfan	
-8	Busulfan	
-7	Busulfan	
-6	Busulfan	
-5	Cyclophosphamide	50 mg/kg/day IV over 1 hour (MESNA; continuous infusion or 5 times daily)
-4	Cyclophosphamide	50 mg/kg/day IV over 1 hour (MESNA; continuous infusion or 5 times daily)
-3	Cyclophosphamide Fludarabine	50 mg/kg/day IV over 1 hour (MESNA; continuous infusion or 5 times daily) 40 mg/m2/day IV over 1 hour
-2	Cyclophosphamide Fludarabine	50 mg/kg/day IV over 1 hour (MESNA; continuous infusion or 5 times daily) 40 mg/m2/day IV over 1 hour
-1	Fludarabine	40 mg/m2/day IV over 1 hour
0		Stem Cell Infusion

4.1 Busulfan: Busulfan (intravenous BUSULFEX) dosing will be as follows: patients ≤ 12 kg: 1.1 mg/kg/dose IV every 6 hours for 16 doses total; patients > 12 kg: 0.8 mg/kg/dose IV every 6 hours for 16 doses. Administration and pharmacokinetic monitoring will be performed as per standard practice. Anticonvulsants will be given in accordance with standard Blood and Marrow Transplant Program recommendations.

4.2 Cyclophosphamide: Cyclophosphamide (50 mg/kg/dose) will be given IV on Days -5, - 4, -3 and -2 over 1 hour. The total dose to be given over 4 days is 200 mg/kg. Mesna will be given in accordance with standard Blood and Marrow Transplant Program recommendations.

4.3 Fludarabine: Fludarabine will be given IV daily over 1 hour for 3 days. Dosing will be as follows: for patients ≤ 10 kg: 1.3 mg/kg; for patients > 10 kg: 40 mg/m^2.

Preparation, administration and monitoring will be according to standard practice procedure.

4.4 Post-Transplant Immunosuppression

4.4.1 CSA will begin on Day -2. The initial dose will be 2.5 mg/kg IV over 2 hours every 12 hours. Dose adjustments will be made to maintain levels above 200 ng/mL. Levels will be done on Day 0 and then as clinically indicated. =CSA will be tapered per institutional SOP. Once the patient can tolerate oral medications and has a normal gastrointestinal transit time, CSA will be converted to an oral form.

4.4.2 MMF will begin on Day 0 at a dose of 15 mg/kg IV or orally tid and will be discontinued on Day +45 unless GvHD is present.

4.5 CNS Disease

Patients with CNS relapse or primary CNS disease that is symptomatic or associated to radiological changes will receive additional irradiation to the craniospinal axis. See Appendix.

4.6 Supportive Care

4.6.1 Supportive care will be provided as per standard practice of the Blood and Marrow Stem Cell Transplant Program at the Texas Children's Hospital, including all prophylactic and therapeutic clinical care issues. These practices may be modified if necessary for any individual patient in order to provide optimum care for that particular patient.

4.6.2 IVIG: Intravenous immunoglobulin (500 mg/kg per dose) will be given monthly until discontinuation of GvHD therapy and documentation of antibody production.

4.6.3 CB-CTLs: Patients enrolled in this protocol may also be eligible for infusion of CB-derived multivirus-specific CTL to provide virus-specific immune reconstitution and treatment of viral infections after CBT.

5.0 EVALUATIONS DURING THE STUDY

5.1 Screening Procedures; Pre-HCT

5.1.1 Physical examination by Pediatric Bone Marrow Transplant physician (includes History, Physical Examination, Weight, Vital Signs, Pulse Ox and Performance Status).

5.1.2 Pregnancy test

5.1.3 Complete blood count with leukocyte differential, C-reactive protein

5.1.4 Lytes/BUN/Cr

5.1.5 Serum chemistries (AST/ALT/Bili/Alb/LDH)

5.1.6 Electrocardiogram

5.1.7 Echocardiograph

5.1.8 PT/PTT/Fibrinogen/Anti-Thrombin III/von Willebrand Factor

5.1.9 Viral tests (HSV, CMV, EBV, HIV, HBsAg, HBcAb, HC, HTLV1/2)

5.1.10 Bone marrow aspirate and biopsy/lumbar puncture within 2-3 weeks of starting conditioning, as clinically indicated.

5.1.11 Renal function (GFR)
5.1.12 Lumbar puncture will be performed to evaluate any evidence of disease recurrence (if previously positive), as clinically indicated.
5.1.13 Pulmonary function test, if applicable.

5.2 Evaluations Between Day 0 and Day 100

5.2.1 Physical examination by Pediatric Bone Marrow Transplant physician on Days 0, 21, 42, 60, 100 (includes History, Physical Examination, Weight, Vital Signs, Pulse Ox [on Day 0 only] and Performance Status)
5.2.2 Complete blood count with leukocyte differential, C-reactive protein on Days 0, 21, 42, 60, 100
5.2.3 Lytes/BUN/Cr on Days 0, 21, 42, 60, 100
5.2.4 Serum chemistries (AST/ALT/Bili/Alb/LDH) on Days 0, 21, 42, 60, 100
5.2.5 Peripheral blood for STRs or FISH analysis for molecular diagnostics around Days 21, 60 and 100
5.2.6 Lymphocyte phenotype testing (CD3, CD4, CD8, CD19 and CD56), other general viral immune reconstitution studies (ex. ELISPOT, spectrotyping), and lymphoproliferative responses will be performed between Day 21-42 and 60-100
5.2.7 Bone marrow aspirate and biopsy for assessment of leukemia status and UCB engraftment between Day 21-42 and will be repeated between Day 90-100 as clinically indicated. Bone marrow DNA specimen submitted to Molecular Diagnostic Laboratory.
5.2.8 Lumbar puncture will be performed on Day 21-42 and Day 90-100 to evaluate any evidence of disease recurrence (if previously positive), as clinically indicated.
5.2.9 Immunoglobulins (IgG, IgA, IgM) will be taken prior to administration of IVIG from Day 60-100.

5.3 Evaluations after Day 100

5.3.1 Physical examination by Pediatric Bone Marrow Transplant physician (includes History, Physical Examination, Weight, Vital Signs, and Performance Status) around 6, 9, 12, 24 and 36 months.
5.3.2 Complete blood count with leukocyte differential, C-reactive protein around 6, 9, 12, 24 and 36 months.
5.3.3 Lytes/BUN/Cr around 6, 9, 12, 24, and 36 months.
5.3.4 Serum chemistries (AST/ALT/Bili/Alb/LDH) around 6, 9, 12, 24 and 36 months.
5.3.5 Peripheral blood with assessment of engraftment by STRs or FISH analysis and enzyme levels (as appropriate) around 6, 12, and 24 or more frequently as clinically indicated.
5.3.6 Echocardiograph with LVEF at 1 year.
5.3.7 Bone marrow aspirate and biopsy assessment of leukemia status and UCB engraftment around 6, 9, 12 and 24 months, as clinically indicated. Bone marrow DNA specimen submitted to Molecular Diagnostic Laboratory.
5.3.8 Lymphocyte phenotype testing (CD3, CD4, CD8, CD19 and CD56), other general viral immune reconstitution studies (ex. ELISPOT, spectrotyping),

and lymphoproliferative responses will be performed around 6, 9, 12 and 24 months after transplant.

5.3.9 Immunoglobulins (IgG, IgA, IgM) will be taken at 6, 9, 12 and 24 months.

5.4 Follow-Up Interval

Patients will be seen in the hospital everyday until discharge. After discharge from the hospital, the patient will be followed in the BMT clinics on a regular basis as recommended by the primary physician.

5.5 Calendar of Study Evaluations

	Pre-UCBT	Day 0	Day 21	Day 42	Day 60	Day 100	M6	M9	M12	M24	M36
Infusion of cells		X									
History	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X
VS	X	X	X	X	X	X	X	X	X	X	X
Pulse Ox	X	X									
Performance Status	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test	X										
PT/PTT/Fibrinogen/ Anti-thrombin III/CRP//von Willebrand Factor	X										
Viral tests (HSV, CMV, EBV, HIV, HBsAg, HBcAb, HC, HTLV1/2,)	X										
Complete blood count with leukocyte differential, C-reactive protein	X	X	X	X	X	X	X	X	X	X	X
Lytes/BUN/Cr	X	X	X	X	X	X	X	X	X	X	X
Serum chemistries - AST/ALT/Bili/Alb/ LDH	X	X	X	X	X	X	X	X	X	X	X
Peripheral blood with Assessment of engraftment by STRs or FISH analysis and enzyme levels (as appropriate)			X		X	X	X		X	X	
Electrocardiogram	X										
Echocardiograph	X								X		
Renal Function (GFR)	X										
Lymphocyte phenotype testing (CD3, CD4, CD8, CD19 and CD56), other general viral immu reconstitution studies (ex. ELISPOT, spectrotyping), and lymphoproliferative responses			X	X	X	X	X	X	X	X	
Immunoglobulins (IgG, IgM, IgA)					X*	X*	X	X	X	X	
Bone marrow aspirate and biopsy assessment of leukemia status and UCB engraftment. Bone marrow DNA specimen submitted to Molecular Diagnostic Laboratory for chimerism studies	X		X**	X**		X**	X	X	X	X	
Pulmonary Function Test, if applicable	X										
Lumbar Puncture - if previous positive	X		X**	X**		X**					

* Immunoglobulin levels (IgG, IgA, IgM) will be taken as scheduled prior to receiving the monthly IVIG.

** Bone marrow aspirate and lumbar puncture will be performed once during these days: 21-42 and 90-100.

6.0 STUDY ENDPOINTS

6.1 Engraftment: Neutrophil and platelet recovery will be analysed separately. Achievement of absolute neutrophil count > 0.5 x 10^9/L and of untransfused platelet count > 20 x 10^9/L on three consecutive days are considered events. Presence of > 95% donor cells will be considered full chimerism by molecular studies (STRs or FISH).

6.2 Overall survival and organ function: 100 days, 1 year and 3 years after UCBT.

6.3 Acute and Chronic GvHD (assessment of severity based on standard criteria).

6.4 Systemic Infections: All microbiology documented infections occurring within 6 months. Viral load will be monitored for CMV, EBV and AdV as institutional protocols. If there is any evidence of infection with these viruses, the patient will be started on medical or cellular therapy.

6.5 Disease-Free Survival: Evaluate the incidence and disease-free survival at 1 and 3 years.

7.0 STUDY DRUGS

7.1 Busulfan

7.1.1 Therapeutic Classification: Bifunctional alkylating agent.

7.1.2 Pharmaceutical Data: Busulfan (Busulfex Injection® Orphan Medical) is supplied as a sterile solution in single-use ampules containing 60 mg at a concentration of 6 mg/mL. It is provided as a mixture of demethylacetamide (DMA) and polyethylene glycol 400 (PEG400).

7.1.3 Solution Preparation: Busulfan solution for injection must be diluted with 0.9% Sodium Chloride Injection (NS) prior to administration. The diluent quantity must be 10 times the volume of busulfan, ensuring that the final concentration is ≥ 0.5 mg/mL. Sample calculation for a 50 kg patient: (50 kg) x (0.8 mg/kg of busulfan) = 40 mg = 6.7 mL; 6.7 mL of busulfan + 67 mL of NS = 74 mL total volume. Final concentration: 0.54 mg/mL.

7.1.4 Stability and Storage Requirements: After dilution with NS or D5W, busulfan is stable at room temperature (25 degrees Celsius) for 8 hours. The infusion must be completed within that time. Prior to mixing: Store under refrigeration (2 to 8 degrees Celsius). Busulfan for injection is stable at 4° for at least 12 months.

7.1.5 Route of Administration: Busulfan should be administered intravenously via a central venous catheter as a two-hour infusion.

7.1.6 Usual Dosage Range: 0.8-1.1 mg/kg/dose given every 6 hours for a total of 16 doses. For patients ≤ 12 kg a dose of 1.1 mg/kg/dose will be used, and for patients > 12 kg the dose will be 0.8 mg/kg/dose. Doses are based on actual body weight, unless the patient's weight is greater than 30% of ideal body weight, then dosing will be based on adjusted weight of ideal plus 25%.

Busulfan pharmacokinetics will be performed on all patients with dose adjustment as appropriate.

7.1.7 Pharmacokinetics: Doses will be adjusted to achieve the desired plasma area under the curve (AUC) of 800 – 1200 μmol-min/L. Doses will be adjusted as necessary pending the results of the first dose pharmacokinetics. For patients whose AUC values are greater than 5% outside the acceptable AUC range, the dose will be adjusted to achieve a target AUC of 1125 μmol-min/L (midpoint of acceptable range) not to exceed a maximum dose of 1.6 mg/kg per dose of busulfan.

7.1.8 Side Effects: Myelosuppression, neurotoxicity (manifesting as seizures), mild to moderate nausea and vomiting, mild to moderate tachycardia, skin hyperpigmentation, sterility, and rarely hepatotoxicity (hepatic veno-occlusive disease) and pulmonary toxicity (interstitial fibrosis).

7.1.9 Special Precautions: Increased toxicity in obese patients unless dose is adjusted appropriately. Generalized seizures have been reported after use of high dose busulfan. All patients will be treated with anticonvulsant therapy while receiving Busulfan. The clinical pharmacist must review orders for anticonvulsants. Blood anticonlvulsant levels should dictate dosing.

7.1.10 Mechanism of Action: Busulfan is a bifunctional alkylating agent in which two labile methanesulfonate groups are attached to opposite ends of a four-carbon alkyl chain. In aqueous media, busulfan hydrolyzes to release the methanesulfonate groups. This produces reactive carbonium ions that can alkylate DNA. DNA damage is thought to be responsible for much of the cytotoxicity of busulfan.

7.1.11 Human Pharmacology: Busulfan can be administered orally or intravenously. Busulfan achieves levels in cerebrospinal fluid similar to plasma levels. Busulfan is predominantly metabolized by conjugation with glutathione, both spontaneously and by glutathione S-transferase (GST) catalysis. This conjugate undergoes further extensive oxidative metabolism in the liver. Approximately 30% of busulfan and metabolites can be recovered in the urine within 48 hours after administration.

7.2 Cyclophosphamide (CTX, Cytoxan) - Commercially Available

7.2.1 Formulation: Injectable form is available as lyophilized cakes containing 100 mg, 200 mg, or 500 mg of active drug and 75 mg of mannitol per 100 mg of active drug in single use vials.

7.2.2 Storage: Cyclophosphamide is to be kept dry and at room temperature until reconstitution and use.

7.2.3 Stability: All preparations are stable at room temperature (not to exceed 30 degrees C). Discard reconstituted solutions after 24 hours at room

temperature; stable up to 6 days if refrigerated (2-8 degrees C). Since there is no preservative, precautions should be taken to insure sterility, or solution should be discarded within 8 hours. The parenteral form of cyclophosphamide prepared as a liquid oral preparation diluted to < 2 mg/mL can be refrigerated (2-8 degrees C) for up to 14 days.

7.2.4 Administration: 50 mg/kg will be given over 1 hour daily for a total of 4 doses. Cyclophosphamide may be diluted in D5NS 200 mL/m².

7.2.5 Toxicities

Known Toxicities

	Common (21-100% Frequency)	**Occasional (5-20% Frequency)**	**Rare (<5% Frequency)**
Immediate:	Anorexia (L), nausea (L), vomiting (L)	Metallic taste (L), Inappropriate ADH secretion1	Transient blurred vision cardiac toxicity with arrythmias[1],myocardial necrosis[2] (L)
Prompt:	Myelosuppression (L), alopecia (L)	Hemorrhagic cystitis (L)	
Delayed:	Immunosuppression, gonadal dysfunction/sterility		Pulmonary fibrosis[3] (L)
Late:			Secondary malignancy, bladder fibrosis
Unknown Timing and Frequency	Fetal and teratogenic toxicities [4,5]		

(L) Toxicity may also occur later
[1] Less common with lower doses
[2] Only with very high doses
[3] Risk increased with chest radiation
[4] Fetal toxicities and teratogenic effects of cyclophosphamide (alone or in combination with other anti-neoplastic agents) have been noted in humans. Toxicities include: chromosome abnormalities, multiple anomalies, pancytopenia, and low birth weight.
[5] Cyclophosphamide is excreted into breast milk. Neutropenia has been reported in breast-fed infants. Cyclophosphamide is considered to be contraindicated during breast feeding because of the reported cases of neutropenia and because of the potential adverse effects relating to immune suppression, growth, and carcinogenesis.

7.3 FLUDARABINE

7.3.1 Therapeutic Classification: Purine antimetabolite.

7.3.2 Pharmaceutical Data: In vials of 50 mg.

7.3.3 Solution Preparation: Reconstituted with 2 mL of sterile water for injection. The resulting solution will contain 25 mg/mL. For infusion (maximum concentration of 10 mg/mL) intravenously in 100 mL of standard intravenous piggy back fluid (dextrose 5%, or normal saline) over 1 hour.

7.3.4 Stability and Storage Requirements: Prior to mixing: Store under refrigeration 2 to 8 degrees Celsius. After mixing: Stable for 16 days at room temperature, but needs to be used in 8 hours because of the lack of antibacterial preservatives.

7.3.5 Routes of Administration: IV infusion.

7.3.6 Usual Dosage Range: For patients ≤ 10 kg: 1.3 mg/kg; for patients > 10 kg: 40 mg/m² IV over 1 hour daily for a total of 3 doses.

7.3.7 Side Effects: Myelosuppression, exacerbation of hemolytic anemia, prolonged immunosuppression, opportunistic infection and rare neurotoxicity.

7.3.8 Special Precautions: Increased myelosuppression in patients with creatinine clearances of less than 50 mL/min.

7.3.9 Mechanism of Action: A purine antimetabolite modified with fluorine and monophosphate to resist deamination by adenosine deaminase and to increased solubility. Dephosphorylation followed by cellular incorporation and conversion to active triphospahte, which is a competitive inhibitor of DNA synthesis.

7.3.10 Antitumor Data: The drug has greater activity to T-cells than B-cells, but clinical activity is observed in B-cell malignancies.

7.3.11 Human Pharmacology: Fludarabine can only be given via intravenous route. Renal excretion accounts for 23%. Half-life is 10 hours.

7.4 MYCOPHENOLATE MOFETIL (MMF): Risks may include upset stomach, including diarrhea and vomiting; risk of serious infections; bleeding and easy bruising; risk of some cancers with long term treatment; risk to baby in pregnancy. It will also cause decrease function on your lymphocytes (immunosuppression).

7.5 CYCLOSPORIN A (CSA): Risks may include acne, dizziness, headache, increased hair growth, nausea, runny nose, sleeplessness, stomach discomfort, vomiting and seizures. It will also cause decreased function on your lymphocytes (immunosuppression).

7.6 IVIG: Risks include headache, myalgia, fever, chills, backache, chest pain, nausea and/or vomiting.

8.0 EVALUATION OF TOXICITIES

The criteria listed in the NCI Common Toxicity Criteria Scale will be used in grading toxicity (Version 4.0 located at http://ctep.cancer.gov). GvHD will be graded by the method of Przepiorka et al. (see Appendix I).

9.0 RISKS

9.1 Leukemia relapse.

9.2 Non-engraftment: One major risk of patients undergoing stem cell transplant for non-malignant diseases is non-engraftment. We are anticipating lower incidence of graft failure or autologous recovery with the use of Fludarabine in our protocol.

9.3 GvHD: Acute GvHD leads to a skin rash, liver dysfunction, and enteritis. GvHD prophylaxis in most types of patients reduces the incidence of grade II-IV GvHD to about 35% with commonly used regimens of today. Recent reports showed an incidence of aGvHD grade III-IV of 10% (Prasad, V. et al. Blood 2008). Chronic GvHD is a multiorgan autoimmune disease usually requiring therapy with steroids and other immunosuppressives. It is seen in about 30% of adults undergoing transplant and lower percentage of children. The risk of cGvHD after UCBT for pediatric diseases have been reported to be as low as 8% (Unpublished data of the University of Minnesota. Martinez, C, Orchard, P., and Tolar, J.).

9.4 Additional Risks: The degree of immune suppression of marrow transplant patients leads to an increased risk of opportunistic infections, especially those due to CMV, HSV, EBV, Pneumocystis, and other viruses and fungi. Prophylaxis is given where possible (Acyclovir, Bactrim, Antifungal, and antibacterial mouth rinses, etc.), and treatment for suspected agents is initiated very promptly, usually before the infection is confirmed. Partial or incomplete T cell function sometimes leads to immune dysregulation and has been associated with autoimmune phenomena in patients with primary immune deficiency. These phenomena include but are not limited to autoimmune hemolytic anemia, neutropenia and thrombocytopenia. These complications may occur as a result of the underlying immune deficiency or from incomplete reconstitution following allogeneic SCT. Other complications of an unexpected nature may be seen. There is a chance that the patient could die from this treatment or from side effects of the treatment such as bleeding or infection. Patients are made aware of this possibility.

10.0 STATISTICAL CONSIDERATIONS

10.1 Sample Size Considerations

The protocol is designed to demonstrate that pediatric patients with myeloid hematological malignancies received umbilical cord blood transplant will have a 1-year overall survival rate of at least 60%. Accrual of pediatric patients with

lymphoid hematological malignancies who are eligible to receive umbilical cord blood transplant is about 2 subjects per year. The accrual period is 10 years with follow-up of at least 2 years or till death for each patient. If we suppose that a true 1-year overall survival rate of 40% would not be unacceptable, then we would need to accrue 20 patients to have 83% power to confirm the clinically meaningful 1-year overall survival rate of 60%. The type-I error is 0.05 with one-sided testing, and the sample size determination was based on the assumptions of uniform accrual, no loss to follow-up and exponentially distributed survival time (30).

10.2 Monitoring Overall Survival and Engraftment

We will monitor grade III-IV GvHD continuously. Accrual to the trial will be halted if the rate of GvHD is estimated to be significantly higher than 10% using a one-sided 2.5% significance level. The choice of 10% aGvHD rate is consistent with the literature as summarized in Section 9.3. Patients will be monitored sequentially. Sequential monitoring will be implemented by a Pocock-type stopping boundary: The rule states that when the second patient finishes toxicity follow-up, if patient 2 had grade III-IV GvHD, then the trial will be halted; for 3rd to 6th enrolled patients who have finished follow-up, the trial will be halted if there are 3 or more grade III-IV GvHD; for 7th to 12th enrolled patients who have finished follow-up, the trial will be halted if there are 4 or more grade III-IV GvHD; for 13th to 17th enrolled patients who have finished follow-up, the trial will be halted if there are 5 or more grade III-IV GvHD; for 18th to 20th enrolled patients who have finished follow-up, the trial will be halted if there are 6 or more grade III-IV GvHD.

Additionally, we will monitor engraftment failures (failure to reach an ANC of 500/μL by Day 42) by employing the group sequential method. Specifically, we will exam the number of engraftment failures 5 times in a group of 4 patients each. The table, below, lists the number of engraftment failures necessary to trigger a suspension of accrual until a thorough reevaluation of the protocol has been completed. Those numbers are determined by the O'Brien-Fleming method to reduce the chance to erroneously suspend the trial early when in fact it is the true rate of engraftment failure is the acceptable 10%. They also increase the chance to suspend the trial early when the true rate of engraftment failure is greater than 10%. The probabilities of trial suspension under three possible rates of engraftment failure (p=0.1, 0.2, 0.3) are also listed in the table below calculated by the exact method using binomial distribution.

Engraftment Failure Safety Monitoring Guidelines (p: true rate of engraftment failure)

# Patients Entered	# Engraftment Failures For Trial Suspension	Prob. To Suspend if p=0.1	Prob. To Suspend if p=0.2	Prob. To Suspend if p=0.3
4	1	0.34	0.59	0.76
8	2	0.19	0.50	0.74

12	2	0.10	0.17	0.16
16	2	0.17	0.21	0.13
20	2	0.19	0.14	0.05

10.3 Statistical Analysis

The primary outcome of overall survival after transplantation will be compared to a fixed null hypothesis 1-year survival rate of 40% by a one-sided test. In addition to the 1-year overall survival, the secondary endpoints included engraftment (neutrophil and platelet), acute and chronic GvHD, disease-free survival, long-term survival, relapse, and regimen-related toxicities. Neutrophil engraftment is defined as the first of 3 consecutive days of achieving an ANC of 500/μL with more than 90% donor cell chimerism. Platelet engraftment is defined as achieving a platelet count of 50,000/μL without transfusion support for 7 days. Primary graft failure is defined as failure to reach an ANC of 500/μL by Day 42. Secondary graft failure is defined as either severe persistent neutropenia unresponsive to growth factor therapy or loss of donor chimerism after initial engraftment. Relapse is defined as more than 25% blasts in the blood or bone marrow or more than 5% blasts in the bone marrow with reappearance of the original cytogenetic abnormality associated with patient's malignancy or more than 5% blasts in the bone marrow on multiple occasions or any extramedullary relapse.

We will calculate Kaplan-Meier estimates and confidence intervals for time to overall survival, disease-free survival and primary graft failure. We will use cumulative incidence curves for engraftment and GvHD endpoints with death as a competing risk. The impact of HLA match, cell dose, race or ethnicity, disease status, age, performance status, risk status, and patient CMV seropositivity will be assessed. We will use the log-rank test for differences in survival between groups in the univariate survival analysis. The Cox proportional hazards model will be used for multivariate analysis of covariates on the main survival endpoints.

We will summarize incidence rates and 95% confidence intervals for engraftment failure, acute GvHD, neutrophil recovery at Day 42 and platelet recovery at Day 180.

11.0 RECORDS TO BE KEPT

The CAGT research nurse/coordinator will maintain a database documenting the dates and doses of therapy as well as clinical chemistries and hematologic parameters. The clinical status and occurrence of any adverse events and subsequent interventions are to be kept on all patients.

Imaging reports
Surgical summaries
Autopsy summaries, where appropriate
Informed consent documents

All required clinical evaluation records will be the responsibility of Dr. Martinez who will also be responsible for analysis of the clinical outcome and toxicity.

The laboratory evaluation of immunological efficacy will be the responsibility of Dr. Martinez.

12.0 REPORTING REQUIREMENTS

12.1 Register all patients with Cell and Gene Therapy Research Nurse.

12.2 Enter all patients by calling Drs. Martinez/Krance. The following forms should be completed:
Eligibility checklist
On study form
Adverse Events Record
Follow-up Forms
Off Study Forms

12.3 Drug Toxicity and/or Adverse Reactions: Adverse events will be collected per SOP J 02.05.XX, J 02.06.XX and J 02.78.XX.

13.0 INFORMED CONSENT

All patients and/or their legal guardian must sign a document of informed consent consistent with local institutional and Federal guidelines stating that they are aware of the investigational nature of this protocol and of the possible side effects of treatment. Further, patients must be informed that no efficacy of this therapy is guaranteed, and that unforeseen toxicities may occur. Patients have the right to withdraw from this protocol at any time. No patient will be accepted for treatment without such a document signed by him or his legal guardian. Full confidentiality of patients and patient records will be provided according to institutional guidelines.

14.0 DATA MONITORING PLAN

This protocol will be monitored in accordance with current Data Safety Monitoring Board Plan for investigator-initiated Phase I and II studies in the Dan L. Duncan Cancer Center at Baylor College of Medicine.
The conduct of this clinical trial will be evaluated in accordance with the Texas Children's Cancer Center and the Center for Cell and Gene Therapy Quality Assurance Policy and Procedure Plan.

15.0 OFF STUDY CRITERIA

- Refusal of further study follow up by patient or legal guardian
- Relapse
- Primary Engraftment Failure
- Acute Graft Rejection
- Lost to follow up
- Completion of Study Procedures and Follow-up
- Death

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APPENDIX I

GVHD STAGES AND GRADES

For skin:	Stage	Skin Involvement
	0	0
	1	greater than 0, less than 25%
	2	greater than or equal to 25%, less than or equal to 50%
	3	greater than 50%
	4	greater than 50% with blisters

For gut:	Stage	Stool Volume
	0	less than 7 cc/kg
	1	greater than or equal to 7 cc/kg, less than 14 cc/kg
	2	greater than or equal to 14 cc/kg, less than 21 cc/kg
	3	greater than or equal to 21 cc/kg, less than 28 cc/kg
	4	greater than or equal to 28 cc/kg

For liver:	Stage	Bilirubin (mg/dL)
	0	less than 2
	1	greater than or equal to 2, less than 3
	2	greater than or equal to 3, less than 6
	3	greater than or equal to 6, less than 15
	4	greater than or equal to 15

Overall:	Grade	Organ Stage
	0	0
	1	skin = 1 or 2
	2	skin = 3, or skin less than or equal to 3 and gut or liver equal to 1
	3	skin greater than or equal to 3 and gut or liver equal to 2 or 3
	4	skin, gut or liver equal to 4

APPENDIX 2

RADIATION GUIDELINES

1.0 CONTINGENCY: CNS RELAPSE OR PRIMARY CNS DISEASE

1.1 It is anticipated that patients with combined CNS/hematologic relapse or isolated CNS relapse will enter the transplant preparative regimen only after clearance of CSF cytology with IT chemotherapy.

1.2 Cranial irradiation will be administered before conditioning in attempting to achieve CNS disease control except in patients < 2 years.

1.2.1 High energy irradiation.

1.2.2 Total dose: 10.8 By mid-plane cranium.

1.2.3 Fractionation: 180 cGy once daily x 6 fractions.

1.2.4 Treatment time: treatment will be completed within 8 calendar days.