Roswell Park Cancer Institute

Protocol Number: **DS 97-26**

Protocol Title: **CORD BLOOD TRANSPLANTATION FOR HEMATOLOGIC MALIGNANCIES AND BONE MARROW FAILURE SYNDROMES**

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Study Duration: 15 years

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1.0 Objectives

1.1 To determine the safety, efficacy and toxicity of using cord blood as a source for stem cell transplantation in patients with hematologic malignancies.

2.0 Background Information

Allogeneic bone marrow transplantation can provide long-term remission or cure for many patients with hematologic malignancies who failed first-line therapy (1). However, the potential for allogeneic bone marrow transplantation is limited in many patients by the lack of either a matched sibling or unrelated donor. Additionally, the risk of graft-vs.-host disease (GVHD) is significant in unrelated donor bone marrow transplants, particularly as the degree of HLA matching decreases to allow for greater numbers of donors. Umbilical cord blood transplantation has been used as an alternate source for stem cells in related and unrelated donor transplants (2-5).

Two primary groups have led the frontier with cord blood transplants. Wagner, et al., at the University of Minnesota have reported on 44 children who have received cord blood transplants from sibling donors for malignant and non-malignant diseases (2). The patients ranged from 8 months to 16 years. Thirty-four patients received HLA-identical grafts, 4 patients received a one-antigen mismatch, 1 patient received a two-antigen mismatch, and 5 patients received a three-antigen mismatched graft. Conditioning regimens varied - 24 patients received chemotherapy and radiation, 19 patients received chemotherapy alone and 1 patient was not identified. GVHD prophylaxis varied as well with cyclosporine (CSA) alone (n=19), CSA plus steroids or anti-T-cell antibody (n=8), CSA with short course methotrexate (n=13), methotrexate alone (n=2), or methotrexate plus steroids or anti-T-cell antibody (n=2). The median time to neutrophil recovery was 22 days, median time to platelet recovery was 49 days. Twenty-seven out of 33 evaluable patients had complete chimerism, 5 patients had mixed chimerism and one patient had autologous recovery. Seven patients had graft failure and either had autologous recovery or received autologous or the same sibling donor marrow infused. Two of these 7 graft failure patients are surviving. The probability of grade II - IV acute GVHD was 3% for HLA-identical or one-antigen mismatch grafts. None of those patients had grade III-IV GVHD. Only one patient with a 3-antigen mismatch developed steroid-resistant grade III acute GVHD. The probability of limited chronic GVHD one year post-transplant was 6%. No patient had extensive chronic GVHD. The probability of survival was 62% with a median of 1.6 years follow-up. For patients with malignant disease, the probability of relapse was 49%.

Kurtzberg, et al, at Duke University have published on 25 patients receiving unrelated umbilical cord blood transplants (3). The patients ranged in age from 0.8 to 23.5 years of age and 7.5 to 79.0 kg. Twenty-four of the patients received a graft mismatched at from one to three antigens. Preparative regimens consisted of mainly total body irradiation, melphalan, and ATG. Busulfan was substituted for irradiation in those patients under 2 years of age. Patients with conditions other than leukemia received a variety of other conditioning regimens, although all but one patient received ATG as part of the regimen. The one patient who did not receive ATG did not engraft (J. Kurtzberg, personal communication). The number of nucleated cells/kg infused ranged from 0.7×10^7 to 11.0×10^7. GVHD prophylaxis consisted of primarily CSA and high-dose methylprednisolone (10 mg/kg initially with tapering). Eleven patients had also received methotrexate, however, none of them developed severe GVHD and this was subsequently discontinued. Twenty-three of the patients engrafted, with a median neutrophil recovery of 22 days, and a median platelet recovery of 56 days. All surviving patients were complete chimeras. Seven patients had grade II acute GVHD, 2 patients had grade III acute GVHD and no patient experience grade IV GVHD. Two patients had limited chronic GVHD involving liver or skin. No patient experienced extensive chronic GVHD. There was no correlation between degree of HLA mismatching and the incidence or extent of GVHD. Twelve of 25 patients had event-free survival between 7 to 32 months. Ten additional patients have received cord blood transplants at their institution and have similar results to the 25 patients published. These last 10 patients have had lower dose methylprednisolone (30 mg/m2 initially with tapering) with CSA for GVHD prophylaxis and have not had an increased incidence or severity of GVHD (J. Kurtzberg, personal communication).

Cyclophosphamide (Cytoxan) and total body radiation have been used extensively as a conditioning regimen at many bone marrow transplant centers, particularly for the acute leukemias (AML, ALL). Cytoxan doses have ranged traditionally from 120-200 mg/kg divided between 2 and 4 days. TBI doses have ranged from 1000-1350 cGy which is frequently fractionated at 150 - 200 cGy fractions. The Cytoxan/TBI regimen for this protocol will use 60 mg/kg of Cytoxan per day for 2 days, followed by TBI at 200 cGy per fraction for 6 fractions (1200 cGy total) in attempt to minimize regimen related toxicity. The combination of Busulfan and Cytoxan as a non-TBI conditioning regimen is also standardly used at many transplant centers, including Fred Hutchinson Cancer Center in Seattle and Johns Hopkins in Baltimore. Doses of Cytoxan used are as stated above with the TBI containing regimens. Busulfan is now standardly used as the intravenous form. Additionally, Busulfan pharmacokinetics are now available so that Busulfan doses can be adjusted to achieve steady-state levels of 600-900 mg/ml. This has been shown to decrease the incidence of veno-occlusive disease, which has previously been associated with Busulfan containing regimens. Anti-thymocyte Globulin (ATG) will be used additionally since Kurtzberg, et al have experience with this, suggesting that engraftment of cord blood is better with the use of ATG (personal communication, Kurtzberg).

3.0 Eligibility Criteria

3.1 Age - 5 years to 50 years old

3.2 Diagnosis –

ALL in 2nd or later remission
ALL in 1st remission with poor prognostic features (Ph+ chromosome)
AML in 2nd or later remission
AML in 1st remission with poor prognostic features (arising from MDS; cytogenetics with -5, -7, +8, 11q23 abnormalities or complex cytogenetics)
AML or ALL refractory to induction or in relapse
CML
Severe aplastic anemia or Fanconi's Anemia
Relapsed Hodgkin's or Non-Hodgkin's Lymphoma (including CLL)
Multiple Myeloma
Myelodysplastic Syndrome

3.3 Prior therapy –

Patients with previous radiation therapy will be allowed to receive TBI as long as the following limits have not been exceeded:

Kidneys - at least one entire kidney must have had no prior radiation
Whole liver - the whole liver must have received less than or equal to 1000 cGy
Whole abdomen - previous whole abdomen radiation therapy of any dose will not be allowed to receive TBI
Small bowel - ≤ 3000cGy
Heart - ≤1800 cGy
Whole lung - patients who have received whole lung radiation will not receive TBI. Patients with a history of XRT to smaller lung fields will be evaluated on an individual basis with the radiation oncologist.
CNS - patients with ≥ 30 Gy to the whole brain or any portion of the spine will not receive TBI. Smaller fields of the brain will be considered on an individual basis with the radiation oncologist.

Patients not eligible for the TBI containing regimen may receive the non - TBI containing regimen.

3.4 Performance status - Karnofsky ≥ 70%

3.5 Laboratory data

PFTs - DLCO and spirometry $\geq$ 60% predicted or exercise pulmonary study with VO_2 max/kg $\geq$ 15 ml/min/kg
MUGA with EF $\geq$ 50%
bilirubin, Alkaline phosphatase, SGOT < 3 x normal
Serum creatinine < 2 x normal or creatinine clearance > 60 ml/min/1.73m2
HIV antibody negative
HBsAg negative

3.6 Infections -

any active bacterial, viral or fungal infection will exclude patients until the infection has been adequately treated and resolved

3.7 Donor –

3.7.1 There must be no suitable family donor matched for 5 or 6 HLA antigens (A, B, DR) and no suitable unrelated donor matched fully for 6 HLA antigens

3.7.2 There must be a cord blood donor identified with either a 4, 5 or 6 out of 6 match with the patient for HLA antigens (A, B, DR)

The cord blood product must provide a minimum of 1 x 10^7 nucleated cells/kg, test negative for HIV and Hepatitis A,B and C, and sterility assays have no growth. The cord blood products are located through the National Marrow Donor Program, the American Registry, or the Bone Marrow Donor Worldwide, and may be stored in the NY Placental Cord Blood Bank, the St. Louis Cord Blood Bank, or any of the established, registered European or Canadian Blood and Marrow Banks

3.8 Informed consent -
Patients must be aware of the malignant nature of their disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side effects, risks, and discomforts.

4.0 Registration and Data Submission

4.1 Registration
Confirm eligibility - contact the Research Nurse to determine transplant regimen.

4.2 Data Submission
Submit forms to the Research Nurse.

5.0 Treatment Plan

5.1 Supportive Care
All patients will receive supportive care following standard BMT care, including PCP prophylaxis, Viral and fungal prophylaxis and G-CSF or GM-CSF.

5.2 GVHD Prophylaxis
FK 506 (Tacrolimus, Prograf) will be used at 0.03 mg/kg as a continuous infusion starting on day –1. Levels will be monitored and kept in the range of 5-15 mg/ml. Patients will be converted to oral dosing (usually 3-4 times the IV dose) once able to tolerate oral fluids and is ready for discharge. Patients will stay on FK 506 for 6 months minimum, longer if necessary to control GVHD.

Solumedrol will be given at 1 mg/kg (0.5 mg/kg BID) on Day +1 to day +4 and 2 mg/kg (1 mg/kg BID) on day + 5 until day +19 or until the first day ANC reaches $\geq$ 500/mm3. After ANCs have reached $\geq$ 500/mm3, steroids should be tapered by 0.2 mg/kg/week. Solumedrol can be given intravenously initially and changed to oral preparation at the same dosing once able to tolerate oral fluids and ready for discharge.

5.3 Preparative Regimen

5.3.1 Cyclophosphamide (Cytoxan)/TBI/ATG

Cyclophosphamide. *Benadryl 25-50 mg should be given 30 minutes prior to the administration of all cyclophosphamide doses.*
IV hydration with D5 1/2 NS at 150ml/m2/hr until urine S.G < 1.012 and urine output $\geq$ 2.5 cc/kg/hr, followed by Cyclophosphamide at 60 mg/kg/dose (lesser of IBW or actual BW is used) in 300 ml/m2 of D5W to run over 2 hours each day on D#-5 and -4. Hyperhydration continues until 24 hours following last dose of cytoxan. Lasix may be given as needed to maintain urine output.

Total body irradiation at 200 cGy BID (minimum of 6 hours between fractions) on D# -3, -2, and -1. Total dose of 1200 cGy in 6 fractions. See Appendix IV for details.

Antithymocyte Globulin (ATG) is given at 30mg/kg (Ideal body weight, or actual body weight, whichever is less)IV on D# -3, -2, and -1. Tylenol (10 mg/kg or 650 mg max), Benadryl (1.25 mg/kg IV or 50 mg max), and solumedrol (2mg/kg)IV will be given prior to ATG. ATG is infused over 10 hours.

5.3.2 Busulfan/Cytoxan/ATG

Busulfan. A minimum of 8-12 hours prior to first dose, begin IV hydration.

INTRAVENOUS ADMINISTRATION: At 0900 hrs on day -7 begin busulfan 0.8mg/kg (ideal body weight or actual body weight, whichever is less (for obese patients, see next paragraph)), over 2 hours IV, q6h for 16 doses (total dose 12.8 mg/kg).

DOSING: Patients will be dosed based on ideal body weight (IBW) or actual body weight (ABW), whichever is lower, and Busulfan levels obtained whenever possible. For obese patients, adjusted ideal body weight (AIBW) should be used, but only if Busulfan levels are obtainable. If Busulfan levels cannot be obtained, obese patients should be dosed by IBW.

Administration of phenytoin. All patients receiving busulfan must receive a loading dose of phenytoin or fosphenytoin. Oral phenytoin is preferred over fosphenytoin. Fosphenytoin should be given if IV dosing is required.

Adult loading dose: phenytoin 1000 mg (PO) in 3 divided doses starting at 6 PM on day -8 (i.e., 300 mg at 6 PM, 300 mg at 9 PM, and 400 mg at 12 MN).
Pediatric loading dose: 15 mg/kg phenytoin in 3 divided doses starting at 6 PM on day –8

Alternatively, fosphenytoin (IV) at 15 mg/kg may be given in 1 dose infused over 60 minutes, starting at 9 PM on day –8. All doses of fosphenytoin will be rounded to the nearest 100 mg. A phenytoin trough level should be drawn prior to the first maintenance dose of phenytoin on the morning of day -7, and additional dosing will be adjusted accordingly, correcting for patients' albumin. Maintenance phenytoin dosing will continue on the morning of Day –7.

Adult maintenance dose: 100 mg PO, TID for a total of 12 doses.
Pediatric maintenance dose: 1.5 mg/kg PO every 8 hours, for a total of 12doses.

The risk of busulfan seizures is higher with repetitive busulfan dosing, however, the busulfan therapy must not be delayed before the level is available as long as the patient receives a loading dose of phenytoin and is continued on maintenance therapy.

In addition: It will be the clinician's decision to substitute alternative anti-seizure agents if required.

Cyclophosphamide. *Benadryl 25-50 mg should be given 30 minutes prior to the administration of all cyclophosphamide doses.*
IV hydration with D5 1/2 NS at 150ml/m2/hr until urine S.G < 1.012 and urine output ≥ 2.5 cc/kg/hr, followed by Cyclophosphamide at 60 mg/kg/dose (lesser of IBW or actual BW is used) in 300 ml/m2 of D5W to run over 2 hours each day on D#-3 and -2. Hyperhydration continues until 24hours following last dose of cytoxan. Lasix may be given as needed to maintain urine output.

ATG 30 mg/kg (Dose based upon the lesser of either ideal body weight or actual body weight) IV on D# -3, -2 and -1. Tylenol (10mg/kg or 650 mg max po), Benadryl (1.25 mg/kg IV or 50 mg max) and solumedrol (2 mg/kg IV) will be given 30 minutes prior to ATG). ATG will be infused over 10 hours.

5.4 Stem Cell Preparation and Reinfusion

Cryopreserved units of cord blood stem cells will be shipped to Roswell Park in liquid nitrogen in vapor phase and stored in liquid nitrogen prior to patients receiving their preparative regimen. The cord blood product is then thawed at the time needed for reinfusion and infused intravenously into the patient.

Cord blood units will not be T-cell depleted, volume reduced or depleted of red cells.

6.0 Drug Formulation

6.1 Cytoxan (Cyclophosphamide) is commercially available in 100, 200, 500 and 1000 mg vials. Dilute with 5, 10, 25 or 50 ml, respectively, of Sterile water for Injection, yielding a concentration of 20 mg/ml which is stable for 24 hours at room temperature. Give the appropriate IV dose by 2 hr infusion after further dilution to 500 ml with D5W.

6.2 Busulfan is commercially available in 10 ml. single-use ampules each containing 60 mg. busulfan at a concentration of 6 mg/ ml. for IV use. IV busulfan should be diluted with 0.9% NaCl or 5% Dextrose Injection, U.S.P. Mixed solution is stable for 8 hours at room temperature (25° C), but the infusion must be completed within that time. Busulfan diluted in 0.9% NaCl is stable under refrigeration (2-8° C) for up to 12 hours, but the infusion must be completed within that time.

6.3 Anti-Thymocyte Globulin (ATG) is commercially available in 5 ml ampules containing 50 mg of horse gamma globulin/ml. It should be stored in a refrigerator (2-8° C). It should be diluted in 0.9% NaCl and is stable for 24 hours when diluted. ATG should be administered alone.

7.0 Potential Toxicity

7.1 **Toxicity Grading** - See Appendix III for bone marrow transplant criteria. GVHD grading will follow standard published Bearman grading criteria for BMT patients.

7.2 **Hematologic**: Four to six weeks of pancytopenia are expected, and rarely patients may fail to engraft. Blood product transfusions will be given to maintain hemoglobin and platelet counts. All blood products will be irradiated (2500cGy) to prevent GVHD. Broad spectrum antibiotics will be initiated at the time of first fever.

7.3 **Hepatic**: Moderate toxicity is common (grade 1-2). More severe, potentially fatal toxicity can occur, usually in the form of veno-occlusive disease (VOD). Management of liver toxicity is with standard supportive care, and the use of heparin or low-molecular weight heparin for VOD prophylaxis. With either preparative regimen, the incidence of fatal liver toxicity is expected to be < 10%.

7.4 **Pulmonary**: Idiopathic interstitial pneumonitis (IP) is possible after high dose alkylating agent or TBI therapy. Patients with diffuse pulmonary infiltrates often present a diagnostic and management problem. Whenever possible, histologic confirmation should be attempted by broncho-alveolar lavage or trans-bronchial; or open-lung biopsy.

7.5 **Cardiac**: High-dose cytoxan can produce fatal hemorrhagic pancarditis. The risk of fatal cardiac toxicity with this regimen is felt to be < 5%. Patients who develop signs of congestive heart failure not attributable to fluid overload are to be evaluated for carditis prior to additional cytoxan being given. An EKG and echocardiography or MUGA scan should be obtained. If evidence of pericarditis, pericardial effusion or impaired myocardial function is found, no further chemotherapy will be administered.

7.6 **Genitourinary**: Urinary metabolites of cytoxan can produce hemorrhagic cystitis. Microscopic hematuria is common following high-dose cytoxan and up to 20% of patients may have gross hematuria or symptoms. Vigorous hydration prior to and for 24 hours following cytoxan reduces the risk of cystitis. The risk of life-threatening cystitis is < 1%. For patients with a previous cytoxan induced hemorrhagic cystitis, MESNA may be used. Additionally, it is expected that the preparative regimen will cause permanent sterility. All male patients of pubertal age or higher will be offered the option of sperm banking prior to initiating the transplant regimen.

7.7 **Renal**: Mild renal insufficiency is common in patients since they are exposed to many nephrotoxic agents, including antibiotics, amphotericin and cyclosporine. When aminoglycosides are used, serum levels will be monitored. Melphalan in high doses can produce renal toxicity, and this is minimized by vigorous hydration. However, kidney damage may require dialysis, although it is usually reversible.

7.8 **Gastro-intestinal**: Many patients will experience severe toxicity (grade 3-4) for nausea, vomiting and mucositis. Vigorous anti-emetic regimens will be given (e.g., droperidol, ondansentron, ativan, benadryl, reglan, and/or decadron). Additionally, many patients may require parenteral narcotics for mucositis, as well as persistent IV hydration.

Most patients respond to symptomatic diarrhea therapy (e.g., Imodium), after infectious causes are excluded.

7.9 **Skin**: Generalized erythroderma with painful palms and soles may occur, with superficial desquamation. Topical steroid creams may provide symptomatic relief. Long-lasting hyperpigmentation may follow resolution of erythroderma.

7.10 **Hair**: All patients will experience total, reversible alopecia

7.11 **GVHD**: Standard unrelated bone marrow transplant patients have been reported to have an incidence of GVHD as high as 80%, with severe (grade 3-4) GVHD as high as 40-50%. Additionally, a chronic form of GVHD can occur in approximately 40% of patients that survive beyond 3 months. Approximately 1/3 of these may cause significant disability. However, cord blood transplantation has been shown to have a significantly decreased risk of both acute and chronic GVHD, despite HLA-disparity. The risk of GVHD in these patients is expected to be < 20%. Cyclosporine and steroids will be used for front-line prevention and treatment.

7.12 **Allergy**: ATG may be associated with a serum sickness like reaction with rash, hives, pruritis, and joint aches. More severe anaphylactic like reactions with bronchospasm and shock are uncommon but reported. Prior to administration, patients will be pretreated with Tylenol, Benadryl and Solumedrol. Epinephrine and resuscitation equipment will be available at the bedside during administration.

7.13 **Secondary malignancy**: Exposure to alkylating agents and radiation increases the risk of developing leukemia or a second cancer.

7.14 **Risk of Peripheral Blood Stem Cell Harvesting**: The toxicities are related primarily to the venipuncture and the pheresis procedure during which time the patient may experience symptoms of hypocalcemia due to the anticoagulant (citrate). These toxicities may include paresthesia, syncope or vertigo, infection, drug allergy, hemorrhage or air embolism. These are similar potential toxicities to a normal platelet donor.

7.15 **Toxicity Reporting**: Expected toxicity is to be recorded in patient charts. Any fatal toxicity, or grade 3 or higher non-hematologic toxicity should be reported within 7 days to the IRB and protocol coordinator.

DATA AND SAFETY MONITORING PLAN

The Principal Investigator (PI) will be responsible for continuous monitoring of the safety of the study. This monitoring is accomplished by the following:

Patient Outcomes Rounds are held weekly on the transplant unit, at which time all BMT patient care is reviewed, including:

- medications (chemotherapy for conditioning regimens; prophylactic, empiric and therapeutic antimicrobials; graft-versus-host disease prophylactic and therapeutic medications; and possible drug interactions).

- adverse events and/or adverse reactions to any medication, procedure, or other treatment; reports are filed according to RPCI policy and procedure.
- regimen-related toxicity, based on Bearman toxicity grading, and/or Common Toxicity Criteria (CTC) if the toxicity does not correlate with a Bearman grade.
- indications for additional testing or therapies such as biopsies, scans or x-rays.
- a properly signed and dated transplant consent.
- compliance issues that could compromise patient safety; pretransplant, a conference is held for all allogeneic patients for the purpose of describing the need for allogeneic patients to obtain lodging within a 30 mile radius of the hospital and to have a caregiver present at all times while the patient is an outpatient. In addition, psychosocial evaluations are completed on all allogeneic and high-risk autologous transplant patients prior to transplant, to identify any compliance issues.
- other aspects of safety monitoring as prescribed by the BMT Standards of Care and common clinical practice. These include daily physical examinations, clinical laboratory testing, routine surveillance cultures, therapeutic drug level monitoring (i.e., Busulfan, Vancomycin, FK506, Tobramycin, Cyclosporine). Patients who have been discharged from the hospital are monitored in the BMT Clinic until all transplant-related issues are resolved and they are returned to the care of their referring physicians.

The BMT Quality Assurance plan requires quarterly reporting to the BMT Quality Assurance Committee, which in turn reports to the hospital Quality Assurance Committee. Indicators for BMT patient safety monitoring include:

- Patient complaints
- Adverse events and serious adverse events
- Bearman and CTC toxicity grades 3 and 4
- Variances in the delivery of standard care
- Readmissions prior to day +100 post transplant
- Deaths occurring prior to day +100 post transplant
- Engraftment

Follow-up on all transplant patients is continued even after they have returned to the care of their referring physicians. A Long Term Transplant Clinic has been established, which provides care for allogeneic patients with chronic complications, as well as assessments to identify dental, bone, and psychosocial complications.

All outcomes are reported to the Center for International Blood and Marrow Transplant Research (CIBMTR), the Autologous Bone Marrow Transplant Registry (ABMTR), and the National Marrow Donor Program (NMDP). Registry reports are reviewed internally prior to submission to the respective registry. These data are also entered into the RPCI BMT Database, from which patient outcomes are assessed and reviewed on a regular basis. Regimen-related toxicities reported in this fashion have resulted in a number of changes to transplant protocols since 1997, thus decreasing toxicity and improving outcomes in a number of patient groups.

Registry reports also establish the efficacy of treatment as measured by overall best response to transplant at day +100 and on subsequent annual reports. The patients'

medical records serve as original source documents for all reporting. Audits are conducted every two to three years by the CIBMTR and ABMTR, and the NMDP.

8.0 Required Data

8.1 Patients must stay in the Buffalo area (within 30 miles) for at least the first 100 days post transplant, and then return as needed.

8.2 Record on the patient flow sheets: hematologic recovery endpoints (day ANC > 500/*u* l, > 1000 /*u* l; Platelets > 25,000, > 100,000; Hgb > 10 gm%; day of last platelet transfusion and last RBC transfusion), days of occurrence of severe toxicity (grade 3 or 4).

8.3

Tests/Observations	Pre-Rx	Post-Rx***	Post-Disch
Signed Informed Consent	x	--	--
Ht/Wt/ /BSA	x	--	--
Ideal Body Wt/Adjusted Body Wt (if applicable)	x	--	--
Serology (Infectious disease screening)	x	--	
HLA-Class I and II typing	x	--	--
Cr Clearance	x	--	--
PFT's/DLCO/DLVA	x	--	--
ABG's	x	--	--
MUGA or ECHO	x	--	--
EKG	x	--	--
Quantitative Ig's	x	--	--
BM aspirate, biopsy*	x	as clinically indicated	
Staging profile** then as	x	repeat positive studies d+100 and d+360; clinically indicated	
Chimerism	x	d+100	as clinically indicated
CBC/Plt	x	q day to PMN>500, Plt>20K, then as clinically indicated	
Urinalysis	x	as clinically indicated	--
PT-INR	x	as clinically indicated	--
Full Chemistry Panel	x	biw as clinically indicated	
Chest X-ray	x	as clinically indicated	--
Performance Status	x	qwk as clinically indicated	
Toxicity (Bearman and CTC)	--	weekly	q1mo until nl

§ d 0 is day of marrow transplant; studies to be obtained as close to indicated time as possible
* Obtain cytogenetics if previously abnormal
**Non-invasive studies including: (1) measurement (perpendicular diameters) of palpable disease, (2) CT scan of chest, abdomen, pelvis, (3) Whole-body Ga scan (SPECT, if available)
***Post therapy is defined as until engraftment and /or discharge from hospital.
Intervals shown are the minimum requirement

9.0 Response Criteria

9.1 Complete Response (CR):

M1 marrow status with normal blood counts. Mild anemia (Hgb > 9 gm%), leukopenia (WBC > 3000/*u* l), neutropenia (ANC > 1000 / *u* l) and thrombocytopenia (platelets > 50,000/*u* l) are permitted. Patients with cytogenetic abnormalities must also have a normal karyotype. Patients with aplastic anemia must be transfusion independent. For patients with lymphoma, there must be no evidence of disease (e.g., all CT scans negative and gallium and bone scans negative)

9.2 Partial Response (PR):

Blood counts as for a CR, but bone marrow has > 5% blasts or persistent cytogenetic abnormality. If patient has aplastic anemia, must be transfusion independent, but with moderate pancytopenia (Hgb > 8 gm%, WBC > 500/*u* l and platelets > 20,000/*u* l). For patients with lymphoma who have disease at time of transplant, there must be at least a 25% reduction in the size of the lesion or adenopathy, and or improvement noted on a bone scan or gallium scan.

10.0 Statistical Considerations

10.1 Study Design

This is a phase II feasibility study of high dose therapy and cord blood stem cell transplantation for patients with hematologic malignancies or severe aplastic anemia who would otherwise receive an allogeneic bone marrow transplant (sibling or unrelated) if a donor were available. Response rates will be determined for each disease based upon the preparative regimen. Toxicity analysis will combine disease categories within each preparative regimen for analysis.

10.2 Endpoints

The primary goal is to determine the efficacy of using cord blood as a source of stem cells for allogeneic transplantation. Overall response rate, 2, 3 and 5 year progression-free survival for each regimen will be estimated in each strata for each disease. The frequency and degree of nonhematologic toxicity will also be examined.

10.3 Sample Size

Target accrual for the CyATGTBI regimen is 20 patients; target accrual for the BuCyATG regimen is 10 patients, for a total study accrual of 30 patients. We anticipate approximately 2 patients per year accrual.

10.4 Stopping Criteria

Entry of patients will be suspended before full accrual if treatment related deaths occur at an unacceptable rate. A sequential stopping rate will be used. If the number of toxic deaths (regimen-related) exceeds the number in the table below at any given point,

accrual will be suspended for that regimen and the toxicity will be considered unacceptable. This stopping rule is based on a sequential probability ratio test with Type I and type II error rates set at alpha = 0.05 and beta = 0.01, and the null and alternative toxicity rates set at $P_0 = 0.10$ and $P1 = 0.25$. If the observed number of toxic deaths is greater than or equal to the number in the table, then it can be concluded with 99% power that the toxic death rate is greater than an unacceptable rate of 25% and the study should be stopped.

No. Patients	3	6	12
Unacceptable	3	4	5

11.0 References

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Appendix I:
Toxicity Criteria

Regimen Related Toxicity in Patients Undergoing BMT (Bearman)

	Grade I	Grade II	Grade III
Cardiac	Mild EKG abnormality, not requiring medical intervention; or noted heart enlargement on CXR with no clinical symptoms	Moderate EKG abnormalities requiring and responding to medical intervention; or requiring continuous monitoring without treatment; or congestive heart failure responsive to digitalis or diuretics	Severe EKG abnormalities with no or only partial response to medical intervention; or heart failure with no or only minor response to medical intervention; or decrease in voltage by more than 50%
Bladder	Macroscopic hematuria after 2 days from last chemotherapy dose with no subjective symptoms of cystitis and not caused by infection	Macroscopic hematuria after 7 days from last chemotherapy dose not caused by infection; or hematuria after 2 days with subjective symptoms of cystitis not caused by infection	Hemorrhagic cystitis with frank blood, necessitating invasive local intervention with installation of sclerosing agents, nephrostomy or other surgical procedure
Renal	Increase in creatinine up to twice the baseline value (usually the last recorded before start of conditioning)	Increase in creatinine above twice baseline but not requiring dialysis	Requirement of dialysis
Pulmonary	Dyspnea without CXR changes not caused by infection or congestive heart failure; or CXR showing isolated infiltrate or mild interstitial changes without symptoms not caused by infection or congestive heart failure	CXR with extensive localized infiltrate or moderate interstitial changes combined with Dyspnea and not caused by infection or CHF; or decrease of PO2 (>10% from baseline) but not requiring mechanical ventilation or > 50% O2 on mask and not caused by infection or CHF	Interstitial changes requiring mechanical ventilatory support or >50% oxygen on mask and not caused by infection or CHF
Hepatic	Mild hepatic dysfunction with bili > 2.0 mg% but < 6.0 mg %; or weight gain > 2.5 % and < 5 % from baseline of noncardiac origin; or SGOT increase more than 2-fold but less than 5-fold from lowest preconditioning	Moderate hepatic dysfunction with bili >6 mg% < 20 mg %; or SGOT increase with > 5-fold from preconditioning; or clinical ascites or image documented ascites > 100ml; or weight gain > 5% from baseline of noncardiac origin	Severe hepatic dysfunction with bili > 20 mg %; or hepatic encephalopathy; or ascites compromising respiratory function
CNS	Somnolence but the patient easily arousable and oriented after arousal	Somnolence with confusion after arousal; or other new objective CNS symptoms with no loss of consciousness not more easily explained by other medication, bleeding, or CNS infection	Seizures or coma not explained by other medication, CNS infection, or bleeding
Stomatitis	Pain and/or ulceration not requiring a continuous IV narcotic drug	Pain and/or ulceration requiring a continuous IV narcotic drug	Severe ulceration and/or mucositis requiring preventive intubations; or resulting in documented aspiration pneumonia with or without intubations
GI	Watery stools > 500 ml but < 2,000 ml every day not related to infection	Watery stools > 2,000 ml every day not related to infection; or macroscopic hemorrhagic stools with no effect on cardiovascular status not caused by infection; or sublets not related to infection	Ileus requiring nasogastric suction and/or surgery and not related to infection; or hemorrhagic enterocolitis affecting cardiovascular status and requiring transfusion

NOTE: Grade IV regimen-related toxicity is defined as fatal toxicity

Appendix II:

Guidelines for Total Body Irradiation

1. **Equipment:**
   1. Modality: External photon irradiation
   2. Energy: Use radiation of megavoltage quality: i.e., cobalt-60 or accelerator beams with nominal energy of no less than 4 Mev. High energy photons (6 Mev and above) must satisfy the same total dose requirements for skin surfaces. It will be necessary for each institution to establish through experimental measurements whether the combination of entrance plus exit beams satisfy these conditions in the first few millimeters of tissue.
   3. Geometry: Single or double head treatment units may be used. Dynamic or static fields may be used. The treatment configuration shall be such that the patient is entirely included within the treatment beam exclusive of the penumbra (i.e., the patient shall be situated well within the 90% decrement line at each depth; the 90% decrement line is defined as a line in each plane perpendicular to the central axis connecting points which are 90% of the central axis dose in that plane). It is essential that agreement between the light and radiation fields be established and verified for the extended TBI treatment distance.
   4. Dose Rate: The dose rate shall be between 5 and 25 cGy/min. defined at mid-plane.
   5. Treatment Volume: The patient shall be entirely included within the static or sweeping treatment beam. Care should be taken to guarantee that no part of the patient extends into the penumbra region of the beam.
2. **Treatment Dose:**
   1. Prescription Point is defined as the point midplane at the level of the umbilicus.
   2. Dose Definition: The dose shall be defined as centigray to muscle. No inhomogeneity corrections shall be made in the calculation of the dose to the prescription point.
   3. Total Treatment Dose:
      1. For protocol doses of 1000 or 1200 cGy the total treatment dose shall be delivered in fractions of 200 cGy using a hyperfractionated regimen of 2 fractions per day on 3 consecutive days, with a minimum interval of 6 hrs between fractions.
      2. The protocol total dose of 300 cGy shall be delivered in a single dose fraction
   4. Patient may be treated in any position that is compatible with the homogeneity requirements and allows for the reproducibility of setup and patient dosimetry. The patient shall be treated with arms along the sides and with hands placed flat against the thighs. The patient treatment position should be recorded and submitted as part of the quality assurance documentation.
   5. Tissue compensators may be used when necessary to improve dose homogeneity. If used, a complete description of compensation technique and its effect on the prescription dose and dose distribution shall be reported and submitted as part of the quality assurance documentation.
   6. Skin bolus such as blankets or other body covers may be used to bring up the superficial dose to satisfy the homogeneity requirements. The superficial dose shall be determined at a depth of 2-3 mm.
   7. All fields should be treated each fraction
   8. Lung shielding will be used.
3. **Calculations and Treatment Planning:** It is recommended that the calculational method be based upon measurements that are made in a unit density phantom 35 x 35 x 35 cm3 in size. All measurements should be made at the appropriate TBI extended SSD. The method of calculation should be specific to the institution's methods and clearly documented.

Appendix III:

Definitions: On/Off Study dates, On/Off Treatment dates

On-Study Date	Start Treatment Date	Stop Treatment Date	Off-Study Date
Date conditioning regimen started	Date conditioning regimen started	Date infusion of stem cells is complete (relevant for patients who have more than one over 2 or more days)	Date of first disease progression post-transplant or date of death due to any cause or date patient failed to engraft