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Transplantation of Umbilical Cord Blood in Patients with Hematological Malignancies Using a Reduced-intensity Preparative Regimen

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1. Introduction

Conventional myeloablative allogeneic hematopoietic stem cell transplantation (HCT) is limited by lack of rapidly available HLA matched donors and excess transplant related mortality (TRM). Umbilical cord blood (UCB) is an alternative hematopoietic stem cell (HSC) source with the advantages of relative tolerance of HLA disparity [1-5] and rapid availability [6]. UCB transplantation (UCBT) is a standard therapy for pediatric leukemia [2-5] and is now being investigated in adults [7-10]. Many older patients, or those with extensive prior therapy or serious comorbidities, are unable to tolerate conventional myeloablative conditioning. Therefore, reduced intensity conditioning (RIC) regimens have been developed to extend the possibility of curative transplantation to these populations. The use of either related or unrelated volunteer donors as a graft source for RIC is well established [11-19]. However, for older or infirm patients lacking a suitable related or unrelated donor, UCB is an attractive graft source.

Emerging data suggests that RIC is feasible in the UCB setting [20-25]. Multiple centers have reported pilot studies of UCB RIC, and the University of Minnesota has recently published outcomes in a larger cohort of 110 patients [26]. Optimal conditioning regimen and post-transplantation immunosuppression designed to minimize graft failure and TRM, however, have not yet been defined. This protocol will help clarify these questions by replacing ATG in the conditioning regimen of our current UCB RIC Protocol (FHCRC 2012) with alternative intensification of therapy and by prolonging mycophenolate mofetil (MMF) treatment in the post-transplantation period.

2. Background

At the FHCRC, our conditioning regimen for UCB RIC for patients with advanced or high risk hematologic malignancies has been identical to that of the recently published Minnesota cohort, and we have performed 13 transplants to date. Conditioning includes a single dose of cyclophosphamide (CY) 50 mg/kg on Day –6, fludarabine (FLU) 40 mg/m^2 daily x 5 days (Days –6 to –2), and a single dose of 2 Gy of total body irradiation (TBI) (Day –1) (CY/FLU/TBI). Equine anti-thymocyte globulin (ATG) is administered 30 mg/kg daily on Days –3 to –1 to patients at high risk for graft rejection (those patients who have not undergone autologous transplant within the last year and who have not received combination chemotherapy in the preceding 4 months or have received only a single induction regimen for leukemia or MDS prior to transplantation). Our post-grafting immunosuppression is modified from the Minnesota regimen. Both regimens include cyclosporine (CSA) from Day -3 through Day +100 then tapered 10% per week to be discontinued no sooner than 6 months post-transplant. However, in contrast to Minnesota, which has reported on using MMF only twice daily from Days -3 to 30, the FHCRC regimen includes MMF one gram three times daily from Day 0 to 30.

The Minnesota group developed its current RIC regimen through clinical experience. Its initial RIC regimen included busulfan (BU) 2mg/kg every 12 hours x 4 (Days -8 to -7), FLU 40 mg/m^2 daily x 5 days (Days –6 to –2), and a single dose of 2 Gy of total body irradiation (Day –1) (BU/FLU/TBI). Twenty-one patients were treated on this regimen. Forty-three percent received two cord units at transplant and median infused cell dose was 2.6 total nucleated cells (TNC)x10^7/kg (range 1.6-3.8). The regimen resulted in prolonged neutropenia, and four patients who had experienced no

chemotherapy in the four months preceding RIC experienced donor graft failure. In an attempt to achieve equivalent or greater immunosuppression with less myelosuppression, BU was replaced with a single dose of CY resulting in the CY/FLU/TBI regimen. The change resulted in a significant decrease in median time to neutrophil recovery (9.5 days (range 5-28 days)) and only one graft failure among the first 21 evaluable patients. Sixty-eight percent received two cord units at transplant and median infused cell dose was 3.2 TNCx10^7/kg (range 1.1-5.1). The single CY/FLU/TBI patient with graft failure had advanced myelofibrosis without prior combination chemotherapy [20]. As a result of these observations, ATG was added to the conditioning regimen for patients without combination chemotherapy in the preceding 4 months or with only a single induction regimen for AML prior to transplant. Since the introduction of ATG, engraftment in this high risk group has increased from 64% to 84% in Minnesota's experience [personal communication].

In the recent report of 110 patients using the current CY/FLU/TBI +/- ATG regimen, Minnesota reports 92 percent neutrophil recovery at a median of 12 days (range 0-32) and primary and secondary graft failure in 7 and 8 patients respectively. For the entire cohort, the cumulative incidence of sustained engraftment (neutrophil recovery with complete chimerism) was 85% (95%CI 77-92). Eighty-five percent of patients received two units and the median infused cell dose was 3.7 TNCx10^7/kg (range 1.1-5.3). Three year survival was 45% (95%CI 34-56) and three year event free survival was 38% (95%CI 28-48). Transplant related mortality was 19% (95%CI 12-26%) at day 180 and 26% (95%CI 18-34) at three years. The cumulative incidences of grade II-IV and grade III-IV acute GVHD at day 100 were 59% (95%CI 49-69%) and 22% (95%CI 14-30). Cumulative incidence of chronic GVHD was 23% (95%CI 15-31) at 1 year. In Cox regression analysis; patients with pre-existing high risk clinical features and grade III-IV acute GVHD had a significantly higher relative risk of death (relative risk 3.0 (1.7-5.2, $p<0.01$) and 1.9 (1.0-3.5, $p=0.04$) respectively). In Cox regression analysis, absence of ATG in conditioning regimen was associated with a higher risk of GVHD (relative risk 2.2 (1.2-4.0, $p<0.01$), while in univariate analysis use of ATG was associated with a higher risk of TRM at 180 days (38% vs. 12%, $p=0.02$)[26].

Our limited experience (13 patients to date) makes drawing conclusions based on our own data difficult. With an average follow-up of 463 days among survivors, 4/13 (31%) remain alive, and all results appear consistent with those reported in the larger Minnesota series. Our experience combined with Minnesota's data raise important questions about possible treatment regimen changes that may improve outcomes in RIC UCBT. ATG was originally added to the Minnesota regimen to decrease graft failures in high risk patients, but a number of considerations raise questions about the importance of ATG in the regimen. Four of the first five graft failures in the Minnesota RIC experience occurred following BU/FLU/TBI conditioning. Recent data from Duke and MD Anderson suggest that BU/FLU is associated with unexpectedly high rates of graft failure in the UCBT setting [27, personal communication]. Early graft failures in the Minnesota RIC setting may, therefore, have been a result of the BU/FLU/TBI regimen, and it is unclear the extent to which ATG added to CY/FLU/TBI has enhanced engraftment. In addition, UCB unit selection strategies and post-transplantation immunosuppression practiced at the FHCRC may enhance engraftment rates as compared to the Minnesota experience. Though Minnesota did not report infused cell doses associated with graft failures in their pre-ATG patients, infused cell dose has been established as critical to engraftment rates. To ensure adequate cell doses we have developed a conservative algorithm at the FHCRC such that single unit CBT is allowed only for units matched for 4/6 HLA with TNC dose of at least 6.0

$x10^7$/kg, for 5/6 HLA with TNC dose of at least 4.0 $x10^7$/kg or for 6/6 HLA with TNC at least 3.0 $x10^7$/kg. If these criteria are not met, double unit RIC transplants are performed with a minimum TNC of at least 3.0 $x10^7$/kg. In addition, at the FHCRC we perform pre-transplant panel reactive antibody (PRA) screening followed, in positive cases, by analysis of individual HLA antigens to identify patients at risk for antibody mediated rejection of cord units. To our knowledge this process is not widely performed at other centers, and in 36 patients treated in our recent protocols, four patients have been identified as having units at risk for antibody rejection. For two patients, at-risk units were successfully replaced with alternative safe donor units. For one patient, no safe units could be identified and the patient's donor was switched to a B allele mismatched unrelated donor. The fourth patient was infused one safe unit and one at-risk unit because no alternative donors were available. Though engraftment of the safe unit occurred, the at-risk unit was never seen on post-transplant chimerism analysis, possibly as a result of immediate rejection by an antibody mediated process. Finally, in contrast to Minnesota, at the FHCRC we dose MMF three times daily. Previous data from our center in the unrelated RIC setting has demonstrated a decreased risk of graft rejection when MMF is administered three times rather than twice daily [28]. Using this approach, we have observed one graft failure in 10 evaluable RIC UCB patients and no graft failures in 29 evaluable myeloablative UCBT patients. The RIC patient who experienced graft failure was an AML patient who received ATG during conditioning. She was successfully salvaged with a second double cord transplant using FLU 200mg/m2, CY 50mg/kg, and 4 GY TBI for conditioning. Eight of thirteen RIC patients have received ATG in their conditioning regimen.

While stringent requirements for cell dose, careful assessment of risk for antibody mediated rejection, and three times daily MMF through Day 30 likely contribute to the high rates of engraftment in our collective UCBT experience, RIC patients at high risk for graft failure still may require more significant immunosuppression in their conditioning regimen. For several reasons, however, we believe that ATG poses a particular hazard to this population. ATG is well documented to delay T cell recovery following transplantation and to increase risk of viral infection. Even in the absence of ATG, cord blood patients are known to experience delayed immune reconstitution [29]. Furthermore, our three times daily MMF dosing schedule increases risk of infection compared to Minnesota's twice daily schedule [28]. In the recent Minnesota series, ATG was, in univariate analysis, associated with a higher risk of TRM at 180 days. Among UCBT patients receiving RIC conditioning, ATG has been specifically associated with an increased risk of EBV post-transplant lymphoproliferative disorder (PTLD) [30]. Though anecdotal, in our center's UCBT experience, our only death from CMV (pneumonia) and our only case of HHV6 encephalitis occurred in patients receiving RICs which included ATG in conditioning. In addition, we have observed 100% early CMV reactivation in all UCBT recipients who were seropositive prior to transplant, and ATG likely exacerbates this problem. ATG may also abrogate nascent GVL effects. Finally, ATG is a toxic drug associated with high rates of infusion associated reactions and serum sickness, and though again anecdotal, in our experience one patient scheduled for UCBT RIC died of a myocardial infarction and multi-system organ failure on Day -3 following an adverse reaction to ATG.

For these reasons we propose a stepwise alternative conditioning escalation strategy that does not include ATG for patients at high risk for rejection. Limited literature from several Japanese pilot studies confirms the feasibility of non-ATG based conditioning regimen. Reported regimens include 150 mg/m2 FLU, 80 mg/m2 melphalan (MEL), and 4 Gy TBI as well as 50 mg/kg CY, 200 mg/m2

FLU, and 3 Gy TBI regimen[21,24]. Both of these regimen have been associated with reasonable engraftment, but infused cell doses and post-grafting immunosuppression were varied, and details of outcomes of patients at high risk for rejection were not reported.

We propose a strategy similar to that of FHCRC Protocol 1949 in the unrelated RIC setting. We will replace ATG with an increase in TBI from 200 cGy to 300 cGy.

The removal of ATG from our conditioning regimen does raise concerns about the possibility of increased GVHD and, possibly, subsequent increased mortality. In the Minnesota series, ATG was associated with decreased GVHD, and Grade III/IV GVHD was a risk factor for increased mortality. However, the Minnesota post-transplantation immunosuppression regimen may not be optimal. Patients on the Minnesota regimen received MMF 1 gram twice daily from Days –3 to 30. As described above, we have incorporated three times daily MMF into our post-transplantation immunosuppression regimen. In addition to promoting engraftment, data from Minnesota suggests that TID dosing may decrease the risk of GVHD (though we have not observed this finding in our clinical experience) [31,28]. We also propose extending MMF treatment to Day +40 post-transplantation with a subsequent 12% dose reduction every one week with a stop date anticipated approximately day +96. In our RIC UCBT experience to date, 7/9 evaluable patients have developed grade II-IV GVHD and 3/9 patients developed grade III-IV GVHD. 4/9 evaluable patients discontinued MMF on day 30 with no evidence of GVHD, but three subsequently developed acute GVHD before day 100. Notably, two developed symptoms within a week of stopping MMF. We believe, therefore, that extended MMF may decrease incidence of acute GVHD. Our proposed regimen is consistent with the current unrelated donor RIC MMF schedule under investigation in protocol 1641. In addition, due to possible added toxicity without benefit, MMF dosing will be changed from starting on Day 0 to starting 4-6 hours after infusion of stem cells on Day 0.

Patients deemed at higher risk for graft failure will be enrolled. This group includes patients who have received < 2 cycles of multiagent chemotherapy and patients who have received no multiagent chemotherapy within the 3 months previous to UCBT. Patients experiencing graft failure following previous allogeneic transplant will also be included. Patients who have had previous autologous transplant within 12 months of UCBT are excluded regardless of history of recent treatment.

3. Objectives

The primary objective of this protocol is to better assess efficacy of RIC UCBT as measured by probability of 1 year survival. In addition, a primary objective is to optimize a non-ATG based conditioning regimen. The proposed conditioning regimen will continue to use CY 50mg/m2 and FLU 200 mg/m2, but the initial TBI dose will be increased from 200 cGy to 300 cGy.

A. Primary Objective:

1. Estimate probability of one year survival

2. Demonstrate equivalent or improved engraftment rates with a non-ATG based conditioning regimen. Patients will be considered graft failure/rejections provided they meet any of the criteria listed below:
    i. Absence of 3 consecutive days with neutrophils ≥500/ul combined with host CD3 peripheral blood chimerism ≥ 50% at day 42
    ii. Absence of 3 consecutive days with neutrophils ≥500/ul under any circumstances at day 55
    iii. Death after day 28 with neutrophil count <100/ul without any evidence of engraftment (< 5% donor CD3)
    iv. Primary autologous count recovery with < 5% donor CD3 peripheral blood chimerism at count recovery and without relapse

B. Secondary Objectives:

1. Six month non-relapse mortality
2. Overall incidence of graft failure/rejection. Patients will be considered graft failure/rejections provided they meet any of the criteria listed below:
    i. Absence of 3 consecutive days with neutrophils ≥500/ul combined with host CD3 peripheral blood chimerism ≥ 50% at day 42
    ii. Absence of 3 consecutive days with neutrophils ≥500/ul under any circumstances at day 55
    iii. Death after day 28 with neutrophil count <100/ul without any evidence of engraftment (< 5% donor CD3)
    iv. Primary autologous count recovery with < 5% donor CD3 peripheral blood chimerism at count recovery and without relapse
3. Kinetics of chimeric reconstitution
4. Incidence of neutrophil engraftment by Day 42
5. Incidence of platelet engraftment by six months
6. Incidence of grade II-IV and III-IV acute GvHD at day 100
7. Incidence of one year chronic GvHD
8. Incidence of clinically significant infections at 6 months, 1 year, 2 years
9. Probability of one and two year survival
10. Incidence of one and two year relapse or disease progression
11. Kinetics of immune reconstitution, with both functional and quantitative assays
12. Examination of possible immunologic factors leading to emergence of a dominant unit

4. Patient Selection

A. Inclusions

1. Age, Organ Function and Performance Status Criteria (all patients)

    a. Patients must be <70 years old. Patients > 70 may be considered if Performance Status > 80% or ECOG ≤1 and Comorbidity Score < 3 (Appendix V). These

patients must be discussed with the PI, Rachel Salit (phone 206-667-1317, pager 206-314-2845, prior to enrollment.

b. Adequate cardiac function defined as absence of decompensated congestive heart failure, or uncontrolled arrhythmia and:
   i. left ventricular ejection fraction $\geq$ 35% or
   ii. fractional shortening >22%

c. Adequate pulmonary function defined as DLCO > 30% predicted, and absence of O_2 requirements.

d. Adequate hepatic function. Patients with clinical or laboratory evidence of liver disease will be evaluated for the cause of liver disease, its clinical severity in terms of liver function, histology, and the degree of portal hypertension. Patients with fulminant liver failure, cirrhosis with evidence of portal hypertension or bridging fibrosis, alcoholic hepatitis, esophageal varices, a history of bleeding esophageal varices, hepatic encephalopathy, or correctable hepatic synthetic dysfunction evidenced by prolongation of the prothrombin time, ascites related to portal hypertension, bacterial or fungal abscess, biliary obstruction, chronic viral hepatitis with total serum bilirubin > 3mg/dL, and symptomatic biliary disease will be excluded.

e. Adequate renal function defined as creatinine $\leq$ 2.0 mg/dl (adults) or creatinine clearance > 40 ml/min (pediatrics). All adults with a creatinine > 1.2 or a history of renal dysfunction must have estimated creatinine clearance > 40 ml/min.

f. Performance status score: Karnofsky (for adults) $\geq$ 60 or ECOG 0-2; Lansky (for children) score $\geq$ 50 (Appendix I)

g. If recent mold infection, e.g., *Aspergillus,* must be cleared by infectious disease.

h. Second hematopoietic cell transplant: Must be $\geq$ 3 months after prior myeloablative transplant.

i Patients who have received < 2 cycles of multiagent chemotherapy and patients who have received no multiagent chemotherapy within the 3 months previous to UCBT as well as patients experiencing graft failure following previous allogeneic transplant.

2. Disease Criteria

The following diseases will be permitted although other diagnoses can be considered if approved by PCC and the principal investigators.

a. Acute Myeloid Leukemia/Acute Lymphoblastic Leukemia, including Biphenotypic Acute Leukemia or Mixed-Lineage Leukemia: Must have < 5% morphologic marrow blasts in an evaluable marrow (>25% of normal cellularity for age) collected less than one month prior to start of conditioning. Patients persistently aplastic for greater than one month since completing last chemotherapy are also eligible with the approval of the PI or designee.

b. Chronic myelogenous leukemia: All types, except refractory blast crisis. Chronic phase patients must have failed or been intolerant to Gleevec or other tyrosine kinase inhibitors. At time of transplant, patients must have <5% blasts in an

evaluable marrow (>25% of normal cellularity for age) by morphology within the bone marrow

c. Myelodysplastic syndrome (MDS): Any subtype. Morphologic blasts must be less than 5% in an evaluable marrow (>25% of normal cellularity for age). If blasts are 5% or more, patient requires induction chemotherapy pre-transplant to reduce blast count to less than 5%. Patients who have a hypocellular marrow in the absence of excess blasts that is related to the underlying disease or as a result of treatment for MDS may also be eligible with the approval of the PI or designee.

d. Large-cell lymphoma and aggressive T-cell lymphoma: With chemotherapy sensitive disease that has failed autologous transplant or patients who are ineligible for an autologous transplant. Chemotherapy sensitive disease is defined as ≥ 50% reduction in the size of the tumor with the chemotherapy regimen immediately preceding transplant.

e Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL): Must be refractory to fludarabine or fail to have a complete or partial response after therapy with a regimen containing fludarabine (or another nucleoside analog, e.g. 2-CDA, pentostatin) or experience disease relapse within 12 months after completing therapy with a regimen containing fludarabine (or another nucleoside analog).

f. Hodgkin Disease: Must have received and failed frontline therapy.

g. Follicular lymphoma, marginal zone B-Cell lymphoma, lymphoplasmacytic lymphoma, mantle-cell lymphoma, and indolent T-cell lymphomas: Must have progressed with the most recent remission duration being <6 months. Patients with bulky disease should be considered for debulking chemotherapy before transplant. Patients with refractory disease are eligible, unless they have bulky disease and an estimated tumor doubling time of less than one month.

h. Multiple Myeloma: Must have received prior chemotherapy. Consolidation of chemotherapy by autografting prior to nonmyeloablative HCT is permitted.

i. Myeloproliferative syndromes

B. Exclusions

1. Patients with an available 5-6/6 HLA-A, B, DRB1 matched sibling donor.
2. Pregnancy or breastfeeding.
3. Evidence of HIV infection or known HIV positive serology.
4. Uncontrolled viral or bacterial infection at the time of study enrollment.
5. Active or recent (prior 6 month) invasive fungal infection without ID consult and approval.
6. Active central nervous system malignancy
7. Patients who have received ≥ 2 cycles of multiagent chemotherapy within the 3 months previous to UCBT. Patients who have had previous autologous transplant within 12 months of UCBT are excluded regardless of history of recent treatment.

5. Donor Selection

CB donor selection will be based on institutional guidelines and in general should be selected to optimize both HLA match and cell dose. Additionally, CB grafts shall consist of one or two CB donors based on, but not exclusively determined by, cell dose (TNC/kg and CD34/kg), HLA matching and disease status and indication for transplant. Attending preference will be allowed for single versus double unit as well as the degree of mismatching based on patient specific factors, as long as the following minimum criteria are met:

A. HLA matching:
   i. Minimum requirement: The CB graft(s) must be matched at a minimum at 4/6 HLA-A, B, DRB1 loci with the recipient. Therefore 0-2 mismatches at the A or B or DRB1 loci based on intermediate resolution A, B antigen and DRB1 allele typing for determination of HLA-match is allowed.
   ii. HLA-matching determined by high resolution typing is allowed per institutional guidelines as long as the minimum criteria (#A.i., above) are met.

B. Selection of two CB units is mandatory when a single cord blood unit does not meet the following criteria in the table below.

	Single Unit Allowed for:
Match Grade	**TNC Dose**
6/6	$\geq 2.5 \times 10^7$/kg
5/6, 4/6	$\geq 4.0 (\pm 0.5) \times 10^7$/kg

If two CB units are used, the total cell dose of the combined units must be at least 3.0×10^7 TNC per kilogram recipient weight based on pre-cryopreservation numbers, with each CB unit containing a MINIMUM of 1.5×10^7 TNC/kg.

C. The minimum *recommended* CD34/kg cell dose should be 2×10^5 CD34/kg, total dose from a single or combined double.

D. The unmanipulated CB unit(s) will be FDA licensed or will be obtained under a separate IND, such as the National Marrow Donor Program (NMDP) Protocol 10-CBA conducted under BB IND-7555 or another IND sponsored by (1) a participating institution or (2) an investigator at FHCRC.

E. Up to 5% of cord blood product, when ready for infusion, may be withheld for research purposes as long as thresholds for infused TNC dose are met. Thresholds for single unit transplantation are described in 5.B.4. Threshold for double unit transplantation is $\geq 3.0 \times 10^7$/kg. These products will be used to conduct studies involving the immunobiology of double cord transplantation and kinetics of engraftment.

UCB Unit Exclusions

A. Any cord blood units with $<1.5 \times 10^7$ total nucleated cells per kilogram recipient weight.

B. Any cord blood units without full maternal testing and negative results for hepatitis A, B, C, HIV, and HTLV-1 viruses. Any additional available virology results on the unit itself will be reviewed but are not mandated, complete or always available. Cord blood units are presumed to be CMV negative regardless of serologic testing due to passive transmission of maternal CMV antibodies.

6. Evaluation and Counseling of Patient

The patient and donor units will be completely evaluated. The protocol will be discussed thoroughly with patient and caregivers, and all known risks to the patient will be described. The procedure and alternative forms of therapy will be presented as objectively as possible and the risks and hazards of the procedure explained to the patient or, in the case of minors, to the patient's responsible family members. Informed consent from the patient will be obtained using a form approved by the Institutional Review Board (IRB) of the Fred Hutchinson Cancer Research Center.

7. Protocol Registration

Eligible patients will be identified by the Clinical Coordinators Office. Patients will be registered with the Registration Office (206-667-4728) between 8:30 am and 4:00 p.m. Pacific time, Monday through Friday. After hours, the Registration office can be reached by paging (206) 995-7437.

8. Plan of Treatment, Drug Administration

A. Conditioning Regimen

-6	Fludarabine 40 mg/m^2 IV over 1 hour Cyclophosphamide 50 mg/kg IV
-5	Fludarabine 40 mg/m^2 IV over 1 hour
-4	Fludarabine 40 mg/m^2 IV over 1 hour
–3	Fludarabine 40 mg/m^2 IV over 1 hour
–2	Fludarabine 40 mg/m^2 IV over 1 hour
–1	TBI 300 cGy
0	UCB transplant

1. Cyclophosphamide administration.
   a. Cyclophosphamide will be given at 50 mg/kg on Day -6. Doses ≥ 5000 mg are infused IV over 2 hours. Lower doses usually are administered over one hour. Adjusted body weight should be used for calculating initial doses if patient's actual weight is > 100% of ideal body weight.
   b. MESNA will be given for bladder prophylaxis according to institutional guidelines.

2. Fludarabine administration.
   a. Fludarabine will be administered at a dose of 40 mg/m2 IV over one hour once daily on each of 5 consecutive days for a total dose of 200 mg/m2. Patients > 120% of ideal weight, BSA will be calculated using adjusted weight.
   b. Fludarabine dose for adult patients (≥18 years old) with renal impairment (defined as CrCl < 70mL/minute per 24-hour) is 35 mg/m2 daily for five consecutive days given as noted above.
   c. Fludarabine dose may also be reduced to 35 mg/m2 daily if there is prior malignancy involvement of the central nervous system with intrathecal chemotherapy and/or cranio-spinal irradiation.

3. Total Body Irradiation (TBI)
   See Appendix II for radiation guidelines.

B. Immunosuppressive Therapies
Patients will receive prophylaxis for GVHD with 2 drugs as follows:

1. Cyclosporine A
   a. Patients will receive cyclosporine A (CSA) therapy beginning on Day -3 maintaining a trough level between 200 and 400 ng/mL by HPLC analysis (250 and 500 ng/ml by immunoassay). For adults the initial dose will be 2.5 mg/kg IV over 1 hour every 12 hours. For children < 40 kg the initial dose will be 2.5 mg/kg IV over 1 hour every 8 hours.
   b. Dose adjustments will be made on the basis of toxicity and low CSA levels with a trough level of <200 mg/L (HPLC). Once the patient can tolerate oral medications, CSA will be converted to an oral form. CSA dosing will be monitored and altered as clinically appropriate.
   c. Patients will receive CSA until Day +100. If no GVHD, the dose will then be tapered 10% per week starting on Day +101 and discontinued no sooner than 6 months post-transplant.

2. Mycophenolate mofetil (MMF)

   a. Patients will receive MMF at the dose of 15 mg/kg IV (based on adjusted weight) every 8 hours with a maximum of 1 gram/dose starting 4-6 hours after infusion of UCBT on Day 0. If actual body weight is < ideal weight, calculation based on actual weight is allowed. Rounding of the dose to the nearest 250 mg capsule size is also allowed. Once the patient can tolerate oral medications, MMF may be converted to an oral form.
   b. MMF will be given every 8 hrs daily until day 40 post-transplant and then in the absence of GVHD, tapered by 12%/week with MMF discontinued after day + 96.
   c. MMF dosing to be monitored and altered as clinically appropriate.
   d. Markedly low (<40%) donor T cell chimerism after UCBT may indicate impending graft rejection. MMF should be continued at full dose or, if MMF

taper has been initiated, reinstitution of full dose MMF should occur. If MMF has been discontinued, MMF should be reinitiated at full dose.

C. Umbilical Cord Blood Transplant (UCBT)

1. Procedures for requesting, receiving and characterizing the cord blood unit for infusion will be according to institutional protocol.
2. The cord blood unit should be thawed and infused per FHCRC standard practice guidelines. Cord blood products should be infused without delay as soon as the product arrives on the unit.
   a. The thawed product (either one or two units) will be delivered to the patient floor/bedside where the product is double-checked by a nurse with the technologist from the Cellular Therapy Laboratory. Visual inspection of the product is also made at this time. The unit(s) is verified according to 1) the infusion order sheets, 2) the patient's identification number on the cell product, 3) the product (cell) identification number and 4) the patient wrist band.
   b. If the cord blood unit(s) fail to pass inspection or if there is insufficient information to verify the cell product for the patient, notify the Cell Therapy Lab and the PI, Rachel Salit ((206) 667-1317, pager 206-314-2845 immediately.
   c. The goal infusion time of each cord blood unit is 30 minutes, as clinically possible. Pre-medications (if any) prior to cord blood infusion will be at the discretion of the attending. Under no circumstances is the cord blood to be irradiated. No medications or fluids should be given piggyback through the catheter lumen that is being used for cord blood infusion.
   d. The product is infused via IV drip directly into the central line according to standard practice with gravity filtered tubing.
   e. Vital signs should be monitored before beginning the infusion and periodically during administration. Notify the attending physician, fellow or PA immediately if the patient exhibits signs or symptoms of a reaction.
   f. Benadryl, epinephrine, and hydrocortisone should be available at the bedside for emergency use if necessary. Oxygen with nasal prongs for standby use should be present in the room.
   g. If the patient is a double cord blood recipient, the two units may be given consecutively with no wait between infusion of the units. However, infusion of the second unit will **not** begin until any acute toxicities from the first unit have been controlled. The start and stop time of each unit should be recorded on the infusion record.

D. Supportive Care

Patients will receive transfusions, infection prophylaxis, and therapy according to institutional guidelines (Appendix III for FHCRC infection guidelines).

E. Growth Factor Support

Patients will be started on G-CSF support at 5mcg/kg (IV/SQ)(round to vial size) beginning on Day +1 after the UCB infusion and continued daily until ANC > 2500/μL for 2 consecutive days. Once a patient has met these criteria, the ANC will be monitored and G-CSF restarted if ANC falls to < 1000.

F. Management of Pre-engraftment Immune Reactions

A well recognized clinical entity consisting of skin rash, fever, and, often, loose stools and respiratory distress has been noted to occur prior to engraftment among cord blood patients, generally between Days +7 and +21. This clinical syndrome likely involves cytokine activation, and though clinically similar to acute or hyperacute graft versus host disease, it appears to be a distinct entity, "pre-engraftment syndrome." This syndrome is often controlled with brief steroid bursts, thus avoiding a commitment to extended steroid exposure. Patients should be monitored carefully for this syndrome.

If patients have moderate to severe symptoms as described above and alternative etiologies (i.e., infection) have been excluded or are being appropriately evaluated, recommendations for management are:

1. For patients not on steroid therapy when the syndrome occurs: methylprednisolone should be given at 1 mg/kg IV q day for three days. If symptoms have abated, steroids should be stopped. If symptoms persist, 1 mg/kg can be continued through six days then stopped if symptoms have abated. If symptoms persist for more than six days, the patient should be considered to have acute/hyperacute GVHD and should be treated with prolonged steroids as deemed appropriate.

2. For patients already on steroids for other reasons when the syndrome occurs: methylprednisolone should be given at a dose of 3-5 mg/kg IV (max dose 500 mg) q 12 hours x 48 hours, followed by a rapid taper to 1 mg/kg IV q 12 hours. Patients should be weaned after response as tolerated.

9. Evaluation

Refer to FHCRC/SCCA Standard Practice Manual for Pre-Transplant Evaluation Guidelines for Allogeneic Transplant (results of tests and/or procedures conducted as per standard of care for pre-transplant workups may be used for eligibility determination if conducted within an appropriate window prior to screening). See Appendix IV for schedule of study evaluations.

A. Patient Pre-Study Screening and Evaluation Procedures

1. Medical history, allergies, previous chemotherapy, prior radiotherapy, hormonal or immunotherapy and response to treatment, end-organ toxicity and infections.
2. Karnofsky/ECOG or Lansky performance status (Appendix I).
3. Physical examination.
4. Complete blood and platelet count with leukocyte differential.
5. Basic metabolic and hepatic function panels.
6. Urinalysis.
7. Pregnancy test (blood or urine) in females of childbearing potential.
8. Viral titers (HSV, CMV, HIV, HBsAg, HBcAb, HCV, HTLV1/2).
9. PCR for CMV DNA must be done within 2 weeks prior to the start of conditioning.
10. Bone marrow aspirate (and biopsy as clinically indicated) within 30 days prior to conditioning.

11. Electrocardiogram, MUGA or echocardiography with measurement of the left ventricular ejection fraction (LVEF).
12. Chest radiograph and pulmonary function tests. CXR not required if chest CT performed (see 9.A.15).
13. DNA specimen from patient and from UCB unit(s) submitted to Clinical Immunogenetics Laboratory (CIL) for chimerism studies.
14. X-rays and other disease marker evaluations as appropriate for patient diagnosis (Appendix IX).
15. A chest CT without contrast to exclude occult fungal infection prior to transplant for patients with a history of the following:
    - history of MDS or a history of 2 or more consecutive inductions/re-inductions to treat acute leukemia
    - CML blast crisis
    - prolonged neutropenia of at least 2 months immediately preceding transplant
16. Pediatric pretransplant evaluation considerations: for children that are not able to cooperate to have a MUGA and/or pulmonary function tests, an echocardiogram should be attempted and pulse oximetry with exercise tolerance obtained. If not possible at all, it should clearly be documented in the physician's note.
17. Comorbidity Index score to be completed by research staff (Appendix V).
18. Clinical immune reconstitution studies (see section 9.F).
19. Lymphocytes subset enumeration (T cell subset with B and NK cells)
21. Blood Samples for Host and Donor Immunologic Interaction Studies (see section 9.E).
22. Immune Reconstitution Research Study (see section 9.F)

B. <u>Patient Evaluations from Day 0 until Engraftment (through Day 30)</u>

1. Physical examinations daily or as clinically indicated.
2. Complete blood and platelet count daily, or as clinically indicated, until the absolute neutrophil count (ANC) $\geq 5 \times 10^8$/L for 3 consecutive measurements. Leukocyte differential is to be performed daily if WBC count > 500.
3. Basic metabolic panel daily or as clinically indicated (at least twice weekly).
4. CMV PCR surveillance as clinically indicated per institutional guidelines (Appendix III).
5. Urinalysis as clinically indicated.
6. Chest radiographs as clinically indicated.
7. Bone marrow aspirate (+/- biopsy, as clinically indicated) on Day 28 for assessment of underlying disease and UCB engraftment. Day 28 BM specimen submitted for whole bone marrow chimerism studies. Please note if patient is a double cord blood recipient. Other tests on BM that are disease appropriate on Day 28.
8. Day 28 peripheral blood for chimerism studies (as possible sorted for CD3, CD14, CD33, CD56 cells).
9. Peripheral blood for chimerism studies (sorted for CD3, CD14, CD33, CD56 cells) on Day 28.
10. GVHD evaluation (Appendix VI) weekly or as clinically indicated.

11. Additional tests (e.g., X-rays and tumor markers) as clinically appropriate for assessment of underlying malignancy on Day 28 (Appendix IX).
12. Clinical immune reconstitution studies (see section 10.F).
13. Blood samples for Host and Donor Immunologic Interaction Studies (see section 9.E)
14. Immune Reconstitution Research Studies (see section 9.F)

C. Patient Evaluations from Engraftment to Day 100

1. Physical examinations weekly and/or as clinically indicated.
2. Karnofsky/ECOG/Lansky performance once between Day 80 and Day 100 (App.I).
3. Complete blood and platelet count with leukocyte differential at least weekly and/or as clinically indicated.
4. Basic metabolic panel at least weekly and as clinically indicated.
5. CMV PCR surveillance as clinically indicated per institutional guidelines (Appendix III).
6. Urinalysis as clinically indicated (at least once prior to d/c with urine creatinine/albumin ratio).
7. Chest radiographs as clinically indicated.
8. Peripheral blood for chimerism studies (as possible sorted for CD3, CD33, CD56) on Days 56 and 80.
9. Bone marrow aspirate and biopsy on Day 80 (or prior to departure) for all patients for assessment of disease relapse, chimerism and UCB engraftment. Please note if patient is a double cord blood recipient. Other tests on BM that are disease appropriate on Day 80 (Appendix XI).
10. GVHD evaluation (Appendix VI) weekly and as clinically indicated.
11. Clinical immune reconstitution studies (see section 9.F).
12. Blood samples for Host and Donor Immunologic Interaction Studies (see section 9.E).
13. Immune Reconstitution Research Studies (see section 9.F).

D. Patient Evaluations at 6 months, 1 year and 2 years

1. Physical examinations at 6 months, 1 year and 2 years.
2. Karnofsky/ECOG or Lansky performance status (Appendix I) at 6 months, 1 year and 2 years.
3. Complete blood count with leukocyte differential and serum chemistry at 6 months, 1 year and 2 years and as clinically indicated.
4. CMV surveillance as clinically indicated per institutional guidelines (Appendix III).
5. Chest radiographs as clinically indicated.
6. Peripheral blood for chimerism studies (as possible sorted for CD3, CD33, CD56) at 6 months, 1 year and 2 years.
7. Bone marrow aspirate (+/- biopsy, as clinically indicated) at 1 year and, as clinically indicated, at 2 years for assessment of UCB engraftment and evidence of recurrent disease. DNA BM specimen submitted for chimerism studies. Please note if patient is a double cord blood recipient. Other tests that are disease appropriate (Appendix IX).
8. GVHD evaluation (Appendix VI) at 6 months, 1 year and 2 years.

9. Other tests as clinically appropriate for restaging assessment of underlying malignancy at 6 months, 1 year and 2 years and as clinically indicated (Appendix IX).
10. Autopsy report, if available, if death occurs before the 2 year follow-up.
11. Clinical immune reconstitution studies (see section 9.F).
12. Immune Reconstitution Research Studies at 6 months, 1 year, and 2 years (see section 9.F).

E. Host and Donor Immunologic Interaction Studies

For patients 21-30 kg

1. Prior to the start of conditioning (and after consent obtained): 20 ml of peripheral blood will be collected in green top tubes to generate EBV transformed LCL lines from the patient for research studies evaluating donor/host immunologic reactions.
2. Post transplantation on up to five occasions, 20 ml of peripheral blood may be collected in green top tubes to assay for immune mediated responses occurring between the host and donors. The timing of sample collection will be at investigator discretion and research staff will initiate the orders. Once individual engraftment has occurred and to avoid obtaining samples if patients have been placed on steroids for treatment of a GVHD (steroids interfere with the studies).
3. Please send samples to the Delaney Lab D2-335; contact Denise Ziegler (206) 667-5762
4. Samples should be drawn on MONDAY through FRIDAY ONLY.

For patients larger than 30 kg

1. Prior to the start of conditioning (and after consent obtained): 30 ml of peripheral blood will be collected in green top tubes to generate EBV transformed LCL lines from the patient for research studies evaluating donor/host immunologic reactions.
2. Post transplantation on up to five occasions, 30 ml of peripheral blood may be collected in green top tubes to assay for immune mediated responses occurring between the host and donors. The timing of sample collection will be at investigator discretion and research staff will initiate the orders. Once individual engraftment has occurred and to avoid obtaining samples if patients have been placed on steroids for treatment of a GVHD (steroids interfere with the studies).
3. Please send samples to the Delaney Lab D2-335; contact Denise Ziegler (206) 667-5762
4. Samples should be drawn on MONDAY through FRIDAY ONLY.

F. Immune Reconstitution after UCBT

Clinical Studies (to be performed as possible):

1. Quantitative immunoglobulin levels (IgG, IgA, IgM) will be assessed at Day 28, 56, 100, 6 months, 1 year and 2 years.
2. Lymphocytes subset enumeration (T cell subset with B and NK cells) will be assessed pre-transplant and at Day 28, 56, 100, 6 months, 1 year and 2 years.

Research Studies (research blood samples may be used interchangeably, and amount of blood to be drawn may be reduced at the investigator/attending physician's discretion and as dictated by patient safety):

1. Samples will be collected for assessment of post-transplant immune reconstitution baseline prior to the start of conditioning, and then on Day 28, 56, 100, 6 months, 1 year, and 2 years. FHCRC: We will collect blood in a 10mL tube (green top Na Heparin tube will be sent to the Digel Lab). Participating centers: One green top Na Heparin tube will be collected at all time points as possible. Days 28-100 will be batched for shipment at day 100 to FHCRC for analysis. Later time points will be shipped at time of collection. Samples should be shipped MONDAY through THURSDAY only. Main contact: Denise Ziegler, 206-667-5762.

NOTE: In certain clinical circumstances (e.g., relapse or terminal illness) study tests may be omitted at the physician's or PI's discretion.

G. Study Evaluation Windows

The target dates for post-transplant study evaluations are outlined in the table below:

Evaluation Date Post Transplant	**Window**
Day +21	+/-3 days
Day +28	+/-3 days
Day +42	+/- 7 days
Day +56	+/- 7 days
Day +80	+/- 7 days
Day +100	+/- 7 days
Day +180	+/-30 days
1 year	*
2 year	*

*Every effort will be made to complete the 1 and 2 year evaluations as close to these dates as possible, taking into consideration patient's circumstances at these time points.

10. Drugs, Irradiation and Cord Blood Administration - Toxicities and Complications.

Refer to Appendix X for a list of potential adverse events associated or expected with hematopoietic cell transplantation.

A. Treatment-Related Toxicities

For the purposes of this protocol, toxicity will be graded using the modified NCI common toxicity scale (Appendix VII)

1. Potential toxicities associated with the Conditioning Regimen

Cyclophosphamide

Common Occurs in 21-100 people out of every 100	Less Frequent Occurs in 5-20 people out of every 100	Uncommon Occurs in ≤5 people out of every 100
Nausea/vomiting Mucositis Sterility Severe suppression of blood counts Diarrhea Fluid weight gain/edema Alopecia	Hemorrhagic cystitis	Cardiomyopathy Skin rash SIADH (Syndrome of Inappropriate Anti-diuretic Hormone)

Fludarabine

Common Occurs in 21-100 people out of 100	Less Frequent Occurs in 5-20 people out of every 100	Uncommon Occurs in <5 people out of every 100
Severe suppression of blood counts Diarrhea Anorexia Mucositis Nausea/vomiting Stomatitis Osteoporosis Dysuria	Chills Fever GI bleeding Peripheral edema	Neurotoxicity Agitation and confusion Blurred vision Peripheral neuropathy Hearing loss Headache Cerebellar syndrome Blindness Coma Weakness Depression Insomnia Hemorrhagic cystitis (except in FA) Abnormal renal function test Autoimmune hemolytic anemia Deep venous thrombosis Aneurysms Pruritic skin rash Abnormal liver function/Liver failure Constipation Transient ischemic attack Dysphagia Myalgia Arthralgia Renal failure

Total Body Irradiation (TBI)

At the 200 and 300 cGy, side effects are not expected. Nevertheless, there may be fever, alopecia, parotitis, diarrhea, reversible skin pigmentation, mucositis and late effects including

cataract formation, growth retardation, pulmonary damage, carcinogenesis, and sterilization. Those side effects might be more frequently seen in patients given 400 cGy or 450 cGy.

2. Toxicities potentially associated with the infusion of the UCB graft

Potential toxicities associated with the infusion include DMSO toxicity and side effects from red cells. DMSO toxicity and side effect of red cells may include changes in heart rate, rhythm or function, changes in blood pressure, changes in oxygenation, fever, chills, sweats, nausea/vomiting, diarrhea, abdominal cramping, headache, allergic reaction, presence of DMSO taste and odor, hemoglobinuria, and acute renal failure.

3. Potential toxicities associated with Immunosuppressive Therapies

Cyclosporine A

Nephrotoxicity	Thrombotic thrombocytopenic purpura
Seizures	Electrolyte imbalances
Hypertension	Paresthesias/neuropathy
Hirsutism	Gingival hyperplasia
Increased risk of relapse	Increased risk of opportunistic infection

Mycophenolate Mofetil (MMF)

Pancytopenia	Hypertension
Headache	Dizziness
Insomnia	Hyperglycemia
Electrolyte imbalances	Rash
Leg cramps/bone pain	Nausea/diarrhea
Spontaneous abortion	Birth defects
Progressive multifocal leukoencephalopathy	

Toxicities associated with Growth Factor (G-CSF, Neupogen)

Bone pain	Insomnia
Headaches	Dyspnea
Body aches	Rash
Fatigue	Edema
Nausea/vomiting	

11. Protocol Enrollment and Special Considerations

Projected Target Accrual
ETHNIC AND GENDER DISTRIBUTION CHART

TARGETED / PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	Sex / Gender		
	Females	Males	Total
Hispanic or Latino	4	4	8
Not Hispanic or Latino	34	34	68
Ethnic Category Total of All Subjects*	38	38	76
Racial Categories			
American Indian / Alaska Native	2	2	4
Asian	4	4	8
Native Hawaiian or Other Pacific Islander	1	1	2
Black or African American	4	4	8
White	27	29	56
Racial Categories: Total of All Subjects*	38	38	76

12. Guidelines for Serious Adverse Event Reporting

A. Monitoring the Progress of Trial and the Safety of Participants

This is a Phase 2 clinical trial that is monitored by the principal investigator (PI), Rachel Salit, M.D. and a Data Safety and Monitoring Board (DSMB). For FHCRC patients, the PI reviews the outcome of the date for each individual patient on an ongoing basis. The PI of the study will have primary responsibility for ensuring that the protocol is conducted as approved by the Scientific Review Committee and Institutional Review Board. The PI will ensure that the monitoring plan is followed, that all data required for oversight of monitoring are accurately reported to the DSMB and Protocol and Data Monitoring Committee, that all adverse events are reported according to the protocol guidelines, and that any adverse reactions reflecting patient safety concerns are appropriately reported. The PI will personally review with the Research Nurse the clinical course of all the enrolled patients at least twice monthly.

Until October 2018, this was a multi-institution trial with FHCRC serving as the Coordinating Center. In this capacity, the PI obtained copies of all IRB approvals and had the responsibility for receiving the information required for adverse event reporting and safety monitoring from outside sites, and disseminating that information to the appropriate Consortium committees. Written agreements were obtained from all participating sites acknowledging their responsibilities for data and adverse event reporting and agreement to provide records, files, case report forms or any other documents needed to verify compliance. The PI reviewed outcome data for each individual patient at a minimum of 3 months after UCBT. Clinical outcome data were summarized and transmitted from collaborating centers as case report forms (CRFs). When possible, primary source documents regarding patient

outcomes were collected from the collaborating centers. The CRFs were generated from the collaborating centers at defined time points (day 28, day 100, day 180, 1 year and 2 years post-transplant). The local PI reviewed the official CRF and primary source documents. When the CRFs were verified, the data were entered into a central database managed by the FHCRC Coordinating Center.

The DSMB discontinued the review of outcomes when this protocol closed to accrual in August 2018. A dedicated independent DSMB monitored patient safety. The DSMB met at six-month intervals and all outcome data were reviewed including all adverse events reported to the FHCRC along with those officially reported to the FHCRC IRB. The DSMB confirmed whether the trial met any stopping rules and reviewed any patient safety problems necessitating discontinuation of the trial. Reports from the DSMB were submitted to the FHCRC IRB.

B. Reporting of Adverse Events

Adverse events will be collected and graded according to the modified (for HSCT) NCI Common Toxicity Criteria (Appendix VII). Grade 3 or 4 adverse events (or highly unusual grade 2 adverse events), which occur from the start of study treatment (pre-transplant conditioning) through Day +100 post-transplant will be collected on the Case Report Form (CRF). These adverse events, which are observed by the Investigator or reported by the patient, whether or not attributed to the study, will be reported on the CRF. Attributes will include a description, date of onset, maximum severity, and assessment of relationship to the study agent or other suspect agent(s).

Adverse events will be graded according to CTCAE criteria. Association or relatedness to the study agent will be graded as follows: 1 = unrelated, 2 = unlikely, 3 = possibly related, 4 = probably related, and 5 = definitely related.

If a patient experiences relapse or graft failure and goes on to further treatment off protocol, adverse events will no longer be collected with the exception of death. The adverse event reporting in this clinical trial will comply with current FHCRC reporting policy (see Appendix VIII). For patients being cared for at the FHCRC, health care providers communicate with the PI, trial coordinator or research nurses as events occur triggering subsequent reporting. Toxicities meeting the study stopping rule criteria will be reported to the IRB within 10 days of study staff awareness. All other SAEs and deaths, not meeting the expedited reporting criteria, will be reported to the IRB as part of the annual continuation review report to the IRB. Hospitalization, in general, will not be considered a serious adverse event as the majority of patients receiving reduced intensity transplants are hospitalized. Hospitalization will be considered a serious adverse event if it is unexpected or the duration of the hospital stay is unexpected.

Refer to Appendix X for a list of potential adverse events associated or expected with hematopoietic cell transplantation. PI and the research study team have fulfilled all NIH requirements for training in human subjects protection.

C. Plans for assuring data accuracy and protocol compliance

For study enrollment, a signed consent form and eligibility checklist with source documents must demonstrate study eligibility. Fred Hutch Cord Blood Program research staff review CRFs for adherence to the protocol, accuracy, and completeness. The study is monitored under the FHCRC Monitoring Plan. The FHCRC Data and Safety Monitoring Plan details the full scope and extent of monitoring and provides for immediate action in the event of the discovery of major deviations. .

D. Oversight and Review of Safety Monitoring

An annual review of the progress of the study with respect to the monitoring plan will be performed by a Data and Safety Monitoring Committee (DSMC). As part of the annual renewal process, the PI will submit an accounting of patient enrollment and outcomes defining the monitoring plan in sufficient detail as to permit verification of the report through chart audit. The IRB provides a final level of annual review. Approval by the DSMC is a necessary but not sufficient condition for final approval by the IRB. The IRB will review the same continuation application and materials that are reviewed by the DSMC, and make an independent assessment of the progress of the trial and determine whether the perceived risk-benefit ratio continues to be acceptable.

13. Records

Clinical Statistics maintains a patient database at Fred Hutch to allow storage and retrieval of patient data collected from a wide variety of sources. The investigator will ensure that data collected conform to all established guidelines for coding, collection, key entry and verification. Each patient is assigned a unique patient number to assure patient confidentiality. Patients will not be referred to by this number, by name, or by any other individual identifier in any publication or external presentation. The licensed medical records department, affiliated with the institution where the patient receives medical care, maintains all original inpatient and outpatient chart documents. Patient research files are kept in a locked room. They are maintained and supervised by the FHCRC Cord Blood Program. Access is restricted to personnel authorized by the Cord Blood Program.

14. Statistical Considerations

A. Statistical Analyses

The goal of this study is to gain experience in UCBT with the proposed conditioning regimen. One-year overall survival will be considered to be our primary endpoint, but only for purposes of estimation, not hypothesis testing. Given the population of patients being treated, there does not exist a treatment to which this group can be compared since patients will receive the current approach due to the lack of a suitable alternative donor. The primary objective of the current study is therefore not to compare outcome to a benchmark value, but rather to obtain a reasonably precise estimate of one-year survival. The results of this trial will then form the basis for potential future changes.

We propose to enroll 76 patients to the current study. This sample size was not chosen based on any statistical grounds, but represents a balance between the number of patients that can be accrued in a reasonable time frame and a number that will provide meaningful data upon which future trials can be built.

Secondary endpoints will be evaluated and include overall survival (i.e., beyond one year); non-relapse mortality (at 6 months, one year, and overall); incidence of graft failure/rejection; neutrophil and platelet engraftment; acute and chronic GVHD; relapse; progression-free survival; clinically significant infections.

Kaplan-Meier and cumulative incidence estimates will be used to summarize all time-to-event endpoints as appropriate.

15. Termination of study

The study is now permanently closed to accrual and activities are limited to data analysis.

16. References

1. Kurtzberg, J., M. Laughlin, M.L. Graham, et al., *Placental blood as a source of hematopoietic stem cells for transplantation into unrelated recipients.* N Engl J Med, 1996. 335(3): 157-66.
2. Gluckman, E., V. Rocha, A. Boyer-Chammard, et al., *Outcome of cord-blood transplantation from related and unrelated donors. Eurocord Transplant Group and the European Blood and Marrow Transplantation Group.* N Engl J Med, 1997. 337(6): 373-81.
3. Rubinstein, P., C. Carrier, A. Scaradavou, et al., *Outcomes among 562 recipients of placental-blood transplants from unrelated donors.* N Engl J Med, 1998. 339(22): 1565-1577.
4. Rubinstein, P., J. Kurtzberg, F. Loberiza, et al., *Comparison of Unrelated Cord Blood and Unrelated Bone Marrow Transplants for Leukemia in Children: A Collaborative Study of the New York Blood Center and the International Bone Marrow Transplant Registry.* Blood, 2001. 98: 814a.
5. Wagner, J.E., J.N. Barker, T.E. DeFor, et al., *Transplantation of unrelated donor umbilical cord blood in 102 patients with malignant and nonmalignant diseases: influence of CD34 cell dose and HLA disparity on treatment-related mortality and survival.* Blood, 2002. 100(5): 1611-8.
6. Barker, J.N., T.P. Krepski, T.E. DeFor, et al., *Searching for Unrelated Donor Hematopoietic Stem Cells: Availability and Speed of Umbilical Cord Blood versus Bone Marrow.* Biol Blood Marrow Transplant, 2002. 8: 257-260.
7. Laughlin, M.J., J. Barker, B. Bambach, et al., *Hematopoietic engraftment and survival in adult recipients of umbilical-cord blood from unrelated donors.* N Engl J Med, 2001. 344(24): 1815-22.
8. Laughlin, M.J., M. Eapen, P. Rubinstein, et al., *Outcomes after transplantation of cord blood or bone marrow from unrelated donors in adults with leukemia.* N Engl J Med, 2004. 351(22): 2265-75.
9. Long, G.D., M. Laughlin, B. Madan, et al., *Unrelated umbilical cord blood transplantation in adult patients.* Biol Blood Marrow Transplant, 2003. 9(12): 772-80.
10. Barker, J.N., D.J. Weisdorf, T.E. DeFor, et al., *Transplantation of Two Partially HLA-Matched Umbilical Cord Blood Units To Enhance Engraftment in Adults with Hematologic Malignancy.* Blood, 2005. 105: 1343-1347.
11. Giralt, S., E. Estey, M. Albitar, et al., *Engraftment of allogeneic hematopoietic progenitor cells with purine analog-containing chemotherapy: harnessing graft-versus-leukemia without myeloablative therapy.* Blood, 1997. 89(12): 4531-6.
12. Slavin, S., Nagler, A., Naparstek, E., et al, *Nonmyeloablative Stem Cell Transplantation and Cell Therapy as an Alternative to Conventional Bone Marrow Transplantation with Lethal Cytoreduction for the Treatment of Malignant and Nonmalignant Hematologic Diseases.* Blood, 1998. 91(3): 756-763.
13. Childs, R.e.a., *Engraftment Kinetics after Nonmyeloablative Allogeneic Peripheral Blood Stem Cell Transplantation: Full Donor T-Cell Chimerism Precedes Alloimmune Responses.* Blood, 1999. 94(9): 3234-3241.
14. Giralt, S., P.F. Thall, I. Khouri, et al., *Melphalan and purine analog-containing preparative regimens: reduced-intensity conditioning for patients with hematologic malignancies undergoing allogeneic progenitor cell transplantation.* Blood, 2001. 97(3): 631-7.

15. McSweeney, P.A., D. Niederwieser, J.A. Shizuru, et al., *Hematopoietic cell transplantation in older patients with hematologic malignancies: replacing high-dose cytotoxic therapy with graft-versus-tumor effects.* Blood, 2001. 97(11): 3390-400.
16. Chakraverty, R., K. Peggs, R. Chopra, et al., *Limiting transplantation-related mortality following unrelated donor stem cell transplantation by using a nonmyeloablative conditioning regimen.* Blood, 2002. 99(3): 1071-8.
17. Niederwieser, D., M. Maris, J.A. Shizuru, et al., *Low-dose total body irradiation (TBI) and fludarabine followed by hematopoietic cell transplantation (HCT) from HLA-matched or mismatched unrelated donors and postgrafting immunosuppression with cyclosporine and mycophenolate mofetil (MMF) can induce durable complete chimerism and sustained remissions in patients with hematological diseases.* Blood, 2003. 101(4): 1620-9.
18. Maris, M.B., D. Niederwieser, B.M. Sandmaier, et al., *HLA-matched unrelated donor hematopoietic cell transplantation after nonmyeloablative conditioning for patients with hematologic malignancies.* Blood, 2003. 102(6): 2021-30.
19. Giralt, S., B. Logan, M. Zhang, et al., *Non-Ablative or Reduced Intensity Conditioning Regimens With Volunteer Unrelated Donor Progenitor Cell Transplantation: An Analysis from the Center for International Blood and Marrow Transplant Research*
Sergio Giralt,1, Brent Logan,1, Mei-Jie Zhang,1*, Olivia McGaha,1*, Karen Ballen,1, Christos Emmanouilides,1, Rajneesh Nath,1*, Pablo Parker,1, David Porter,1, Brenda Sandmaier,1, Edmund Waller,1, Juliet Barker,1, Steven Pavletic,1, and Daniel Weisdorf,1.* Blood, 2004.
20. Barker, J.N., D.J. Weisdorf, T.E. DeFor, et al., *Rapid and complete donor chimerism in adult recipients of unrelated donor umbilical cord blood transplantation after reduced-intensity conditioning.* Blood, 2003. 102(5): 1915-1919.
21. Misawa M, Kai S, Okada M, et al. *Reduced-intensity conditioning followed by unrelated umbilical cord blood transplantation for advanced hematologic malignancies.* Int J Hematol. 2006;83:74-79.
22. Chao, N.J., Koh LP, Long GD, et al., *Adult recipients of umbilical cord blood transplants afternonmeyloablative preparative regimens.* Biol Blood Marrow Transplant, 2004;10:569-575.
23. Komatsu T, Narimatsu H, Yoshimi A, et al. Successful engraftment of mismatched unrelated cord blood transplantation following reduced intensity preparative regimen using fludarabine and busulfan. Ann Hematol. 2007;86:49-54.
24. Miyakoshi, S., K. Yuji, M. Kami, et al., *Successful engraftment after reduced-intensity umbilical cord blood transplantation for adult patients with advanced hematological diseases.* Clin Cancer Res, 2004. 10(11): 3586-92.
25. Ballen KK, Spitzer TR, Yeap BY, et al. *Double unrelated reduced-intensity umbilical cord blood transplantation in adults.* Biol Blood Marrow Transplant. 2007;13:82-89.
26. Brunstein CG, Barker JN, Weisdorf DJ, et al. *Umbilical cord blood transplantation after non-myeloablative conditioning: impact on transplant outcome in 110 adults with hematological disease.* Blood. Epub ahead of print, June 2007.
27. Horwitz M, Chute J, Gasparetto C, et al. *Myeloablative intravenous busulfan/fludarabine conditioning does not facilitate reliable engraftment of dual umbilical cord blood grafts in adult recipients.* Blood 2007;110:a2007.
28. Maris MB, Sandmaier BM, Storer BE, et al. *Unrelated donor granulocyte colony-stimulating factor-mobilized peripheral blood mononuclear cell transplantation after nonmyeloablative*

conditioning: the effect of postgrafting mycophenolate mofetil dosing. Biol Blood Marrow Transplant. 2006;12:454-465.

29. Komanduri KV, St. John LS, de Lima M, et al. *Delayed immune reconstitution after cord blood transplantation is characterized by impaired thymopoiesis and late memory T cell skewing.* Blood. Epub ahead of print, August 2007.
30. Brunstein CG, Weisdorf DJ, DeFor T, et al. *Increased risk of Epstein-Barr virus associated post-transplant lymphoproliferative disorder after anti-thymocyte globulin non-myeloablative conditioning for umbilical cord blood transplantation.* Blood, 2005;105:a3235.
31. Jacobson P, Rogosheske J, Barker JN, et al. *Relationship of mycophenolic acid exposure to clinical outcome after hematopoietic cell transplantation.* Clin Pharmacol Ther. 2005 Nov;78(5):486-500.
32. Consoli U, El-Tounsi I, Sandoval A, et al. *Differential induction of apoptosis by fludarabine monophosphate in leukemic B and normal T cells in chronic lymphocytic leukemia.* Blood 1998;91(5):1742-8.
33. Gamberale R, Galmarini CM, Fernandez-Calotti P, et al. *In vitro susceptibility of CD4+ and CD8+ T cell subsets to fludarabine.* Biochem Pharmacol 2003;66(11):2185-91.
34. Giaccone L, McCune JS, Maris MB, et al. *Pharmacodynamics of mycophenolate mofetil after nonmyeloablative conditioning and unrelated donor hematopoietic cell transplantation.* Blood 2005;106(13):4381-8.

APPENDIX I: Performance Status Scales

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

Lansky Play Performance Scale	
Score	Description
100	Fully active, normal
90	Minor restrictions in physically strenuous activity
80	Active, but tires more quickly
70	Both, greater restrictions of, and less time spend in play activities
60	Up and around, but minimal active play, keeps busy with quieter activities
50	Gets dressed but lies around much of the day, no active play; able to participate in all
40	Mostly in bed; participates in quiet activities
30	In bed; needs assistance even for quiet play
20	Often sleeping; play entirely limited to very passive activities
10	Unresponsive
0	Dead

APPENDIX II: Guidelines for Total Body Irradiation

All patients who have had previous radiation therapy or TBI will be seen by Radiation Oncology prior to entrance on the protocol for approval for additional TBI. TBI may be delivered by local guidelines provided the effective dose is equivalent to what is recommended in the TBI Guidelines.

Patients ineligible for this protocol include those who have had previous irradiation to areas of the body such that the Radiation Oncologist feels that even a relatively small dose of total body irradiation (TBI) cannot safely be given.

If the patient has previously had total body irradiation (TBI), the radiation oncologist will have the option of deciding whether the patient is still eligible to receive additional TBI. Based on the recommendation of the treating Radiation Oncologist, the patient may be eligible for this protocol with modifications to the beam such that the lungs and or kidneys are partially shielded from the radiation beam. No other organs may be shielded.

Equipment:
Modality:
High-energy photons with energy ≥ 6MV photons should be utilized. Although there is no upper limit on the energy as long as the skin dose requirements can be met, it is recommended that 18MV or lower be used. The selection of energy is determined by the dose uniformity criterion.

Target Volume:
The total body will be treated including the head and feet in one field (except in certain circumstances). Care should be taken to ensure that the patient is entirely within the 90% isodose decrement line of the beam (i.e., not in the penumbra region of the beam).

Target Dose:
The prescription point is defined as the point along the longitudinal axis of the patient at the midline at the level of the umbilicus (see **Point 5**). No tissue inhomogeneity correction will be made in the calculation of dose to the prescription point. The absorbed dose along the patient's head to toe axis (line formed by the intersection of the midsagittal plane and the midcoronal plane) shall be within 10% of the prescribed dose. The dose at selected anatomical points shall be calculated and these calculations are to be submitted as part of the quality assurance. Measurements of patient dimensions needed for the calculation of the prescription dose will be made at the time of the simulation for lung blocks. Measurement and calculations of required monitor units necessary for each treatment will be performed for both the expected upright treatment position (AP-PA fields) and the reclining, lateral decubitus position (AP-PA fields). In the event the patient proves too ill to receive a fraction in the upright position, dose calculation will have been pre-calculated to permit treatment in the lateral decubitus position).

Prescription Point:
1. **Head (Point 1)**: this reference point is defined along the longitudinal axis of the skull at the greatest mid-separation (immediately superior to the nasal bridge). The depth should be taken as midway between the entrance and exit points of the opposed radiation beams.
2. **Neck (Point 2)**: this reference point is defined along the patient's longitudinal axis at the level of C3/C4 (approximate mid-neck, but chosen for the thinnest mid-separation of the neck). The point is taken to be midway between the entrance and exit point of the beam.
3. **Upper Mediastinum (Point 3)**: this reference point is defined along the patient's longitudinal axis at the level of the angle of Louis. The reference point is midway between the entrance and the exit points of the opposed beams.
4. **Lower Mediastinum (Point 4)**: this reference point is defined along the patient's longitudinal axis at the level of the xiphisternal notch. The reference point is midway between the entrance and exit points of the opposed beams
5. **Umbilicus (Point 5)**: THE PRESCRIPTION POINT is defined along the patient's longitudinal axis at the level of the umbilicus. The prescription point is midway between the entrance and exit points of the opposed beams.
6. **Knee (Point 6):** this reference point is defined along the midline in the midplane of the knee at the level of the patella.
7. **Ankle (Point 7)**: this reference point is defined along the midline at the midplane of the ankle at the level of the lateral malleolus.

8. **Shielded Lung Dose (Point 8)**: this reference point is located on the right chest wall under the lung block. It is centered (both medial/lateral and cephalocaudad) under the lung block as projected on the patient's skin. The depth should be taken as midway between the entrance and exit points of the opposed radiation beams. Dose measurements at this location will be taken during a fraction with lung shielding in place.
9. **Unshielded Lung Dose (Point 9)**: This reference point is the same as point 8. Dose measurements at this location will be taken during a fraction without lung shielding in place. The depth should be taken as midway between the entrance and exit points of the opposed radiation beams.

Dose Definition:
The absorbed dose is specified as centigray (cGy)-to-muscle.

The total dose shall be 300 cGy given in a single fraction.

Dose Rate:
A mid-plane dose rate of between 6 and 15 cGy per minute is required.

Dose Uniformity:
The objective is to keep the dose throughout the body, defined to extend to within 2 mm of the skin surface, to at least 90% of the prescription dose. In addition, the brain dose shall not exceed 107% of the prescription dose. For AP/PA treatments, partial transmission lung blocks will be used to limit the overall total lung dose. The dose at the midpoint of the thickest part of the body while in the treatment position should be determined and if necessary, modifications made to the treatment to raise the dose in this region to at least 90% of the prescription dose.
In order to satisfy the requirement that the skin dose at a depth of 2 mm is within at least 90% of the prescription dose, beam spoilers or other equally effective devices should be used. The field size shall be such that no part of the patient extends into the portion of the penumbra region where the dose is less than 90% of the central axis dose.

Treatment Technique:
Patients will be treated using AP/PA fields in an upright seated or standing position in a TBI positioning device. Treatment will be delivered with equally weighted parallel opposed portals, with each treatment including both AP and PA fields. If the patient is unable to tolerate the upright position, acceptable alternate arrangements will include equally weighted AP-PA parallel opposed fields delivered to the patient in a lateral decubitus position on a treatment couch or gurney.
Changes in patient positioning after the patient has started TBI are discouraged. When unavoidable, to ensure compliance to the overall dose and lung shielding parameters, appropriate changes in lung blocking and dose recalculation will be required.
Young patients requiring anesthesia will be treated in an AP/PA configuration at extended distance. If more than a single field is needed to accomplish treatment, the field junction should occur at the level of the thighs and be shifted every 2 fractions.

Dose Calculation for the Prescription Point:
The calculation of the treatment time or the monitor units for the prescribed dose can be carried out using standard techniques. However, TBI presents special problems relative to the routine treatment

situation in that the field sizes are much larger and the treatment distances much longer. The TBI percent depth dose (PDD) or Tissue Maximum Ratio (TMR) and output factors should be measured under TBI treatment conditions for a range of phantom sizes to establish the database for TBI beam-on time calculations or to validate the calculation methodology.
Typically, a calculation methodology will be adopted which uses PDD or TMR and output factors measured under standard conditions but then modified to account for the larger treatment distance. For example, modified values for inverse square corrected percentage depth dose or tissue-air ratios and tissue phantom ratios are necessary for some treatment units when the patient is positioned at a long distance from the photon source and near the floor or one wall of the room. Also, some deviation from an exact inverse square decrease with distance has been demonstrated for certain geometries.
Measurements of dose at the center of a phantom about the size of the typical patient should be performed and compared to the calculated dose. If differences are found, additional correction factors should be introduced to the calculation method.

Critical Organ Dose Points:
The required dose calculations should be performed for the 9 points referenced above. The midline dose at these locations should be recorded on the TBI Summary Form. The dose can be calculated based on the thickness at each location and factors appropriate to the TBI treatment conditions.
It is recommended that entrance and exit TLDs or diodes be placed on the patient at each required dose assessment location. The midline dose can be calculated from these measurements making the appropriate corrections to the readings and then averaging the corrected values.
In younger patients it is also recommended that TLDs or diodes be placed underneath the lung blocks to document the transmission dose and scatter dose.

APPENDIX III: Infection Treatment and Prophylaxis Guidelines

CMV screening and pre-emptive treatment

CMV.pdf

Anti-fungal treatment

Antifungal_Therapy.pdf

PCP prophylaxis

PCP.pdf

HSV and VZV prophylaxis and treatment

HSV and VZV.pdf

APPENDIX IV: Schedule of Study Evaluations

Activity	Screen	Day 1 to engraftment				Days 31-100				Long Term Follow up		
		daily	Weekly	Day 28 (±3 days)	weekly	Day 42 (±7 days)	Day 56 (±7 days)	Day 80 (±7 days)	Day 100 (±7 days)	6 months (± 30 days)	1 year[5]	2 years[5]
Informed consent	X											
Medical history	X											
Physical exam	X	X			X			X		X	X	X
Performance status	X							X (Day 80-100)		X	X	X
Height/Weight	X							X				
GVHD evaluation		X	X		X			X		X	X	X
Adverse events		X			X				X			
CBC with diff	X	X[3]			X					X	X	X
Basic Metabolic Panel	X	X			X					X	X	X
Hepatic Function Panel	X	As clinically indicated or per standard practice										
Viral screening Including CMV PCR	Per standard practice											
CMV Surveillance by PCR	Per standard practice											
Pregnancy test	X											
Bone marrow bx/asp*	X			X				X			X	
Chimerism – BM				X				X			X	X
Chimerism – PB				X			X	X		X	X	X
Host/donor studies (FHCRC)	X	Investigator discretion as described in 9.E										
Urinalysis	X	As clinically indicated or per standard practice										
EKG	X	As clinically indicated or per standard practice										
MUGA or echo	X	As clinically indicated or per standard practice										
Chest x-ray or CT	X	As clinically indicated or per standard practice										
PFT's	X	As clinically indicated or per standard practice										
Disease evaluation	X			X	(and as defined in Appendix IX)			X		X	X	X
IgG, IgA, IgM (as possible)				X			X		X	X	X	X
Lymphocyte panel (as possible)				X			X		X	X	X	X
Immunophenotypic evaluation	X			X			X		X	X	X	X

Check Section 9: Evaluation for details. Every effort will be made to complete the 1- and 2-year evaluations as close to these dates as possible, taking into consideration patient's circumstances at these time points*Bone marrow biopsy as clinically indicated.

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APPENDIX V: The Hematopoietic Cell Transplant-Comorbidity Index (HCT-CI)

Instructions: Circle applicable scores and provide actual value or cause of co-morbidity.

Comorbidities	Definitions	HCT-CI weighted scores	Actual Lab Values/Comments
Arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome, and ventriuclar arrhythmias	1	
Cardiac	Coronary artery disease‡, congestive heart failure, myocardial infarction, or EF≤50%	1	
Inflammatory bowel disease	Crohn's disease or ulcerative colitis	1	
Diabetes*	Requiring treatment with insulin or oral hypoglycemics, but not diet alone	1	
Cerebro-vascular disease	Transient ischemic attack or cerebro-vascular Accident	1	
Psychiatric Disturbance	Depression anxiety requiring psychiatric consult or treatment	1	
Hepatic -mild*	Chronic hepatitis, Bilirubin >ULN- 1.5 X ULN, or AST/ALT >ULN-2.5XULN	1	
Obesity*	Patients with a body mass index > 35kg/ m^2	1	
Infection*	Requiring continuation of anti-microbial Treatment after day 0	1	
Rheumatologic	SLE, RA, polymyositis, mixed CTD Polymyalgia rheumatica	2	
Peptic ulcer*	Requiring treatment	2	
Moderate/severe renal*	serum creatinine>2mg/dl, on dialysis, or prior renal transplantation	2	
Moderate pulmonary*	DLCO and/or FEV, >65%-80% or Dispend on slight activity	2	
Prior solid tumor	*Treated at any time point in the patient's past history, excluding non-melanoma skin cancer*	3	
Heart valve disease*	Except mitral valve prolapse	3	
Severe pulmonary*	DLCO and/or FEV_1 <65% or dyspnea at rest requiring oxygen	3	
Moderate/severe Hepatic	Liver cirrhosis, Bilirubin>1.5XULN or AST/ALT>2.5XULN	3	
Please provide (KPS):	**Karnofksy performance Score=_____%**	**Total Score =_____**	

Completed by (print):_____ Date completed:_____

Signature:_____

*Comorbidity is currently active or patient requires medical treatment +

‡One or more vessel-coronary artery stenosis, requiring medical treatment, stent, or bypass graft

EF indicates ejection fraction; ULN, upper limit of normal; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; CTD, connective tissue disease; DLCO, diffusion capacity of carbon monoxide; FEV_1, forced expiratory volume in one second; AST, aspartate aminotransferase; ALT, alanine aminotransferase

APPENDIX VI: GVHD Staging and Grading

ACUTE GVHD ASSESSMENT

Staging by Individual Organ Involvement

SKIN: measured by rash first appearing generally between 10 and 70 days after transplant. (excludes rashes of known viral or other origin)

Stage	Description
1	Maculopapular rash <25% BSA
2	Maculopapular rash 25 – 50% BSA
3	Generalized erythroderma
4	Generalized erythroderma with bullous formation and desquamation

LIVER*: measured by total serum bilirubin

Stage	Description
1	2.0 – 2.9 mg/dL
2	3.0 – 5.9 mg/dL
3	6.0 – 14.9 mg/dL
4	≥ 15.0 mg/dL

GUT:** includes only diarrhea occurring after Day +21

Score	Adult	Pediatric***
1	upper GI (anorexia, nausea, vomiting) with diarrhea of <1000 mL/day	upper GI (anorexia, nausea, vomiting) with diarrhea of <555 mL/m^2/day
2	1000 – 1499 mL/day diarrhea	556-833 mL/m^2/day diarrhea
3	≥ 1500 mL/day diarrhea	>833 mL/m^2/day diarrhea
4	severe abdominal cramping, bleeding or ileus caused by GVHD	

* In cases where another cause of hyperbilirubinemia antedated the onset of rash, the liver score should be decreased by one stage.

** In cases where peak GI symptoms are exacerbated by a cause other than GVHD, the gut score should be decreased by one stage.

*** Pediatric patients <17 years of age

ACUTE GVHD ASSESSMENT

Overall Grade

The determination of an overall GVHD grade should be based on the organ stage, response to treatment and whether GVHD was a major cause of death.

Overall Grade	Organ Stage	Qualifying Conditions	Additional Qualifying Conditions
I	Stage 1 -2 skin	No liver or gut	Indicates that the prophylactic immunosuppressive regimen was not sufficient to prevent all manifestations of aGVHD.
II	Stage 3 skin or Stage 1 liver or Stage 1 gut	N/A	Indicates that the prophylactic immunosuppressive regimen was not sufficient to prevent all manifestations of aGVHD, but glucocorticoid treatment after the onset of GVHD was generally sufficient to control the disease.
III	Stage 4 skin or Stage 2-4 liver or Stage 2-4 gut	**without** GVHD as a major contributing cause of death	Indicates that the prophylactic immunosuppressive regimen was not sufficient to prevent all manifestations of aGVHD and that additional treatment after the onset of GVHD did not readily control the disease.
IV	Stage 4 skin or Stage 2-4 liver or Stage 2-4 gut	**with** GVHD as a major contributing cause of death	GVHD was resistant to both the prophylactic immunosuppressive regimen and any additional treatment after the onset of the disease.

GVHD Staging and Grading (continued)

CHRONIC GVHD

In the past, any manifestation of GVHD that was present (or continued) at 100 days after HCT or thereafter was arbitrarily defined as chronic GVHD even if the clinical manifestation was indistinguishable from that of acute GVHD. Advances in HCT practice in the past 2 decades have profoundly altered the presentation and natural history of both acute and chronic GVHD and bring previous definitions into question. For instance, acute GVHD may present beyond 3 months in patients who have received reduced-intensity conditioning whereas manifestations of acute and chronic GVHD can be present simultaneously. Therefore, the current consensus is that clinical manifestations, and not the time to symptomatic onset after transplantation, determine whether the clinical syndrome of GVHD is considered acute or chronic.[1]

Chronic GVHD will therefore be defined according to the National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease. Diagnosis of chronic GVHD will require the presence of at least 1 diagnostic clinical sign of chronic GVHD or presence of at least 1 distinctive manifestation confirmed by pertinent biopsy or other relevant tests after the exclusion of other possible diagnoses. Chronic GVHD will be described as mild, moderate, or severe as graded according to the attached Organ Scoring Sheet. Symptoms developing after day 100 but consistent with acute GVHD only will be considered persistent, recurrent, or late-onset acute GVHD. Symptoms consistent with both chronic and acute GVHD occurring after day 100 will be considered overlap chronic GVHD syndrome.

1 Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host-disease: 1. Diagnosis and Staging Working Group Report. Bio Blood and Marrow Transplant 2005;11:945-955.

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Chronic GVHD Organ Scoring Sheet

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: ☐ **KPS ECOG LPS**	☐ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	☐ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	☐ Symptomatic, ambulatory, capable of self-care, >50% of waking hours out of bed (ECOG 2, KPS or LPS 60-70%)	☐ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN *Clinical features:* ☐ Maculopapular rash ☐ Lichen planus-like features ☐ Papulosquamous lesions or ichthyosis ☐ Hyperpigmentation ☐ Hypopigmentation ☐ Keratosis pilaris ☐ Erythema ☐ Erythroderma ☐ Poikiloderma ☐ Sclerotic features ☐ Pruritus ☐ Hair involvement ☐ Nail involvement **% BSA Involved** ☐ ☐ *Abnormality present but NOT thought to represent GVHD*	☐ No Symptoms	☐ <18% BSA with disease signs but **NO** sclerotic features	☐ 19-50% BSA **OR** involvement with superficial sclerotic features "not hidebound" (able to pinch)	☐ >50% BSA **OR** deep sclerotic features "hidebound" (unable to pinch) **OR** impaired mobility, ulceration or severe pruritus
MOUTH *Diagnostic/distinctive features* ☐ Present ☐ Absent ☐ *Abnormality present but NOT thought to represent GVHD*	☐ No symptoms	☐ Mild symptoms with disease signs but not limiting oral intake significantly	☐ Moderate symptoms with disease signs **with** partial limitation of oral intake	☐ Severe symptoms with disease signs on examination **with** major limitation of oral intake
EYES Mean tear test (mm): ☐ >10 ☐ 6-10 ☐ ≤5 ☐ Not done ☐ *Abnormality present but NOT thought to represent GVHD*	☐ No symptoms	☐ Mild dry eye symptoms not affecting ADL (requiring eyedrops ≤ 3 x per day) **OR** asymptomatic signs of keratoconjunctivitis sicca	☐ Moderate dry eye symptoms partially affecting ADL (requiring drops > 3 x per day or punctal plugs), **WITHOUT** vision impairment	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision caused by keratoconjunctivitis sicca
GI TRACT ☐ *Abnormality present but NOT thought to represent GVHD*	☐ No symptoms	☐ Symptoms such as nausea, vomiting,anorexia,dysphagia, abdominal pain or diarrhea without significant weight loss (<5%)	☐ Symptoms associated with mild to moderate weight loss (5-15%)	☐ Symptoms associated with significant weight loss >15%, require nutritional supplement for most calorie needs **OR** esophagea dilation

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
LIVER	☐ Normal LFT	☐ Elevated Bilirubin, AP*, AST or ALT <2 x ULN	☐ Bilirubin >3 mg/dl or Bilirubin, enzymes 2-5 x ULN	☐ Bilirubin or enzymes > 5 x ULN
☐ *Abnormality present but NOT thought to represent GVHD*				
LUNGS ‡ ☐ **PFTs not done** **FEV1** ☐ **DLCO** ☐	☐ No symptoms ☐ FEV1 > 80% **OR** LFS=2	☐ Mild symptoms (shortness of breath after climbing one flight of steps) ☐ FEV1 60-79% **OR** LFS 3-5	☐ Moderate symptoms (shortness of breath after walking on flat ground) ☐ FEV1 40-59% **OR** LFS 6-9	☐ Severe symptoms (shortness of breath at rest; requiring 0_2) ☐ FEV1 ≤39% **OR** LFS 10-12
☐ *Abnormality present but NOT thought to represent GVHD*				
JOINTS AND FASCIA	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	☐ Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	☐ Contractures **WITH** significant decrease of ROM ***AND*** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
☐ *Abnormality present but NOT thought to represent GVHD*				
GENITAL TRACT *Diagnostic/ Distinctive features:* ☐ Present ☐ Absent ☐ Not examined	☐ No symptoms	☐ Symptomatic with mild signs on exam **AND** no effect on coitus and minimal discomfort with gynecologic exam	☐ Symptomatic with moderate signs on exam **AND** with mild dyspareunia or discomfort with gynecologic exam	☐ Symptomatic **WITH** advanced signs (stricture, labial agglutination or severe ulceration) **AND** severe pain with coitus or inability to insert vaginal speculum
☐ *Abnormality present but NOT thought to represent GVHD*				

Other indicators, clinical manifestations or complications related to chronic GVHD (check all that apply):

☐ Weight loss	☐ Bronchiolitis obliterans	☐ Bronchiolitis obliterans with organizing pneumonia	
☐ Esophageal stricture or web	☐ Pericardial Effusion	☐ Pleural Effusion(s)	☐ Ascites (serositis)
☐ Nephrotic syndrome	☐ Peripheral Neuropathy	☐ Myasthenia Gravis	☐ Polymyositis
☐ Malabsorption	☐ Cardiac conduction defects	☐ Coronary artery involvement	☐ Cardiomyopathy
☐ Eosinophilia >500/microliter	☐ Other: _____		☐ **None**

Biopsy obtained: ☐ **Yes** ☐ **No** **Organ system(s) biopsied:** _____ **GVHD confirmed by histology:** ☐ **Yes** ☐ **No**

OVERALL severity of GVHD: ☐ **No GVHD** ☐ **Mild** ☐ **Moderate** ☐ **Severe**

Change from previous evaluation: ☐ **No GVHD** ☐ **Improved** ☐ **Stable** ☐ **Worse** ☐ **N/A (baseline)**

Completed by (print): _____ **Date completed:** _____

Signature: _____

‡ Pulmonary scoring should be performed using both the symptom and pulmonary function testing (PFT) scale whenever possible. When discrepancy exists between pulmonary symptom or PFT scores the higher value should be used for final scoring. Scoring using the Lung Function Score (LFS) is preferred, but if DLCO (carbon monoxide diffusion capacity corrected for hemoglobin) is not available, grading using FEV1 (forced expiratory volume) should be used. The LFS is a global assessment of lung function after the diagnosis of bronchiolitis obliterans has already been established.[28] The percent predicted FEV1 and DLCO (adjusted for hematocrit but not alveolar volume) should be converted to a numeric score as follows: > 80% = 1; 70-79% = 2; 60-69% = 3; 50-59% = 4; 40-49% = 5; < 40% = 6. The LFS = FEV1 score + DLCO score, with a possible range of 2-12.

APPENDIX VII: Adapted from COMMON TOXICITY CRITERIA (CTC)

ALLERGY/IMMUNOLOGY		
Adverse Event	**Grade 3**	**Grade 4**
Allergic reaction/ hypersensitivity (including drug fever)	Symptomatic bronchospasm, requiring parenteral medication(s), with or without urticaria; allergy related edema/angioedema	Anaphylaxis
Vasculitis Requiring steroids	Requiring steroids	Ischemic changes or requiring amputation
Allergy/Immunology – Other (specify):	Severe	Life-threatening or disabling
BLOOD/BONE MARROW		
Adverse Event	**Grade 3**	**Grade 4**
Hemolysis (e.g., immune hemolytic anemia, drug related hemolysis, other)	Requiring transfusion and/or medical intervention (e.g., steroids)	Catastrophic consequences of hemolysis (e.g., renal failure, hypotension, bronchospasm, emergency splenectomy)
For BMT studies, if specified in the protocol. For pediatric BMT studies, if specified in the protocol.	>4 u pRBC in 24 hours >30mL/kg in 24 hours	Hemorrhage or hemolysis associated with life-threatening anemia; medical intervention required to improve hemoglobin Hemorrhage or hemolysis associated with life-threatening anemia; medical intervention required to improve hemoglobin
CARDIOVASCULAR - ARRHYTHMIA		
Adverse Event	**Grade 3**	**Grade 4**
Cardiovascular/Arrhythmia - Other (specify): _____	Symptomatic, and requiring treatment of underlying cause	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
CARDIOVASCULAR – GENERAL		
Adverse Event	**Grade 3**	**Grade 4**
Cardiac left ventricular function	CHF responsive to treatment	Severe or refractory CHF or requiring intubation
Cardiac troponin I (cTnI)	Levels consistent with unstable angina as defined by the manufacturer	Levels consistent with myocardial infarction as defined
Cardiac troponin T (cTnT)	≥ 0.1 - <0.2ng/mL	≥ 0.2ng/mL
Hypotension	Requiring therapy and sustained medical attention, but resolves without persisting physiologic consequences	Shock (associated with acidemia and impairing vital organ function due to tissue hypoperfusion)
Myocarditis	CHF responsive to treatment	Severe or refractory CHF
Pericardial effusion/ pericarditis	With physiologic consequences	Tamponade (drainage or pericardial window required)
Syncope (fainting) is graded in the Neurology category.	-	-
Thrombosis/embolism	Deep vain thrombosis, requiring	Embolic event including

	anticoagulant therapy	pulmonaryembolism
Vein/artery operative injury is graded as Operative injury of vein/artery in the Cardiovascular (general) category. Other (specify):_____		
Cardiovascular/General –	Severe	Life-threatening or disabling
COAGULATION		
Adverse Event	**Grade 3**	**Grade 4**
DIC (disseminated intravascular coagulation) Also consider Platelets. *Note: Must have increased fibrin split products or D-dimer in order to grade as DIC*	Laboratory findings present with no bleeding	Laboratory findings and bleeding
Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura/TTA or hemolytic uremic syndrome/HUS) Also consider Hemoglobin, platelets, creatinine. *Note: Must have microangiopathic changes on blood smear (e.g., schistocytes, helmet cells, red cell fragments).*	Laboratory findings present without clinical consequences Evidence of RBC destruction with creatinine (>3 x ULN) not requiring dialysis	Laboratory findings and clinical consequences, (e.g., CNS hemorrhage/bleeding or thrombosis/embolism or renal failure) requiring therapeutic intervention Evidence of RBC destruction with renal failure requiring dialysis and/or encephalopathy.
Coagulation - Other (specify):	Severe	Life-threatening or disabling
CONSTITUTIONAL SYMPTOMS		
Adverse Event	**Grade 3**	**Grade 4**
Weight gain associated with Veno-Occlusive Disease (VOD) for BMT studies, if specified in the protocol. Also consider Ascites Edema, Pleural effusion (non-malignant).	>10% or as ascites	>10% or fluid retention resulting in pulmonary failure
DERMATOLOGY/SKIN		
Adverse Event	**Grade 3**	**Grade 4**
Erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)	Severe or requiring IV fluids (e.g., generalized rash or painful stomatitis)	Life-threatening (e.g., exfoliative or ulcerating dermatitis or requiring enteral or parenteral nutritional support)
Rash/desquamation associated with graft versus host disease (GVHD) for BMT studies, if	Symptomatic generalized erythroderma or symptomatic macular, papular or vesicular	Generalized exfoliative dermatitis or ulcerative dermatitis or bullous formation

specified in the protocol.	eruption, with bullous formation, or desquamation covering ≥50% of body surface area.	
GASTROINTESTINAL		
Adverse Event	**Grade 3**	**Grade 4**
Ascites (none-malignant)	Symptomatic, requiring therapeutic paracentesis	Life-threatening physiologic consequences
Colitis Also consider Hemorrhage/ bleeding with grade 3 or 4 thrombocytopenia, hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, melena/GI bleeding, rectal bleeding/hematochezia, hypotension.	Abdominal pain, fever, change in bowel habits with ileus or peritoneal signs, and radiographic or biopsy documentation	Perforation or requiring surgery or toxic megacolon
Diarrhea associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol. *For pediatric BMT studies, if specified in the protocol.* Also consider Hemorrhage/ bleeding with grade 3 or 4 thrombocytopenia, hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, pain, dehydration, hypotension.	>1500mL of diarrhea/day *>15mL/kg of diarrhea/day*	Severe abdominal pain with or without ileus
Duodenal ulcer (requires radiographic or endoscopic documentation)	Uncontrolled by outpatient medical management; requiring hospitalization	Perforation or bleeding, requiring emergency surgery
Gastric ulcer (requires radiographic or endoscopic documentation) Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, hemorrhage/bleeding without grade 3 or 4 thrombocytopenia.	Bleeding without perforation, uncontrolled by outpatient medical management; requiring hospitalization or surgery	Perforation or bleeding, requiring emergency surgeryv
Gastritis Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, hemorrhage/bleeding without grade 3 or 4 thrombocytopenia.	Uncontrolled by out-patient medical management; requiring hospitalization or surgery	Life-threatening bleeding, requiring emergency surgery
Pancreatitis Also consider	Abdominal pain with pancreatic enzyme elevation	Complicated by shock (acute circulatory failure)

Hypotension. *Note: Amylase is graded in theMETABOLIC/LABORATORY category.*		
Mucositis *Note: Radiation-related mucositis is graded as Mucositis due to radiation.*	Painless erythema, edema, or ulcers preventing swallowing or requiring hydration or parenteral (or enteral) nutritional support	Severe ulceration requiring prophylactic intubation or resulting in documented aspiration pneumonia
Typhlitis (inflammation of the cecum) Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, hypotension, febrile neutropenia.	Abdominal pain, diarrhea, fever, and radiographic or biopsy documentation	Perforation, bleeding or necrosis or other life-threatening complication requiring surgical intervention (e.g., colostomy)
HEMORRHAGE		
Notes: *Transfusion in this section refers to pRBC infusion.* *For any bleeding with grade 3 or 4 platelets (<50,000), always grade Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia. Also consider Platelets, Transfusion: pRBCs, and Transfusion: platelets in addition to grading severity by grading the site or type of bleeding.* *If the site or type of Hemorrhage/bleeding is listed, also use the grading that incorporates the site of bleeding: NS Hemorrhage/bleeding, Hematuria, Hematemesis, Hemoptysis, Hemorrhage/bleeding with surgery, Melena/lower GI bleeding, Petechiae/purpura (Hemorrhage/bleeding into skin), Rectal bleeding/ hematochezia, Vaginal bleeding.*		
Adverse Event	**Grade 3**	**Grade 4**
Hemorrhage/bleeding with grade 3 or 4 theombocytopenia Also consider Platelets, hemoglobin, transfusion: platelets, transfusion: pRBCs, site or type of bleeding. If the site is not listed, grade as Hemorrhage – Other (specify site):_____ *Note: This adverse event must be graded for any bleeding with grade 3 or 4 thrombocytopenia.*	Requiring transfusion	Catastrophic bleeding, requiring major non-elective intervention
CNS hemorrhage/bleeding	Bleeding noted on CT or other scan with no clinical consequences	Hemorrhagic stroke or hemorrhagic vascular event (CVA) with neurologic signs and symptoms
Hemoptysis	Requiring transfusion	Catastrophic bleeding, requiring major non-elective intervention
Melena/GI bleeding	Requiring transfusion	Catastrophic bleeding, requiring major non-elective intervention
Rectal bleeding/hematochezia	Requiring transfusion	Catastrophic bleeding, requiring major

		non-elective intervention
Vaginal bleeding	Requiring transfusion	Catastrophic bleeding, requiring major non-elective intervention
Hemorrhage – Other (specify site):	Requiring transfusion	Catastrophic bleeding, requiring major non-elective intervention
HEPATIC		
Adverse Event	**Grade 3**	**Grade 4**
Bilirubin Bilirubin associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol.	>3.0 – 10.0 x ULN >6 - <15mg/100mL	>10.0 x ULN >15mg/100mL
INFECTION/FEBRILE NEUTROPENIA		
Adverse Event	**Grade 3**	**Grade 4**
Febrile neutropenia (fever or unknown origin without clinically or microbiologically documented infection).	Present	Life-threatening sepsis (e.g., septic shock)
Infection/Febrile Neutropenia – Other (specify):	Severe	Life-threatening or disabling
NEUROLOGY		
Aphasia, receptive and/or expressive, is graded under Speech impairment in the NEUROLOGY category.		
Adverse Event	**Grade 3**	**Grade 4**
CNS cerebrovascular ischemia	Transient ischemic event or attack (TIA)	Permanent event (e.g., cerebral vascular accident)
Leukoencephalopathy associated radiological findings	Severe increase in SAS; severe ventriculomegaly; near total white matter T2 hyperintensities or diffuse low attenuation (CT); focal white matter necrosis (cystic)	Severe increase in SAS; severe ventriculomegaly; diffuse low attenuation with calcification (CT); diffuse white matter necrosis (MRI)
Seizure(s)	Seizure(s) in which consciousness is altered	Seizures of any type which are prolonged, repetitive, or difficult to control (e.g., status epilepticus, intractable epilepsy)
PULMONARY		
Adverse Event	**Grade 3**	**Grade 4**
Adult Respiratory Distress Syndrome (ARDS)	-	Present
Apnea	Present	Requiring intubation
Carbon monoxide diffusion capacity (DLCO)	>25 - <50% of pretreatment or normal value	<25% of pretreatment or normal value
FEV1	>25 - <50% of pretreatment or normal value	<25% of pretreatment or normal value
Hypoxia	Decreased O2 saturation at rest,	Decreased O2 saturation,

	requiring supplemental oxygen	requiring pressure support (CPAP) or assisted ventilation
RENAL/GENITOURINARY		
Adverse Event	**Grade 3**	**Grade 4**
Creatinine *Note: Adjust to age-appropriate levels for pediatric patients*	>3.0- 6.0 x ULN	>6.0 x ULN
Renal failure	Requiring dialysis, but reversible	Requiring dialysis and irreversible
SECONDARY MALIGNANCY		
Adverse Event	**Grade 3**	**Grade 4**
Secondary Malignancy – Other (specify type): _____ *Excludes metastasis from initial primary.*	-	Present

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PPENDIX VIII: FHCRC IRB Policies

http://extranet.fhcrc.org/EN/sections/iro/irb/policy/index.html

Appendix IX: Recommended Additional Disease Specific Evaluations

Pre-transplantation

Multiple Myeloma (*Waldenstrom's Macroglobulinemia patients, same as below with no skeletal survey, or MRI):

- Complete skeletal survey including skull and long bones
- MRI of skeleton
- Quantitative serum immunoglobulin levels
- Serum protein electrophoresis and immunofixation
- 24hr urine collection to determine creatinine clearance and protein excretion, urine protein electrophoresis and immunofixation
- Serum cryoglobulins
- C-reactive protein
- Serum ß2 microglobulin
- Serum viscosity for patients with > 3.0 mg/dl of IgM monoclonal protein or > 4.0 mg/dl of IgA or IgG protein
- FISH probes for chromosome 13 abnormalities.

Lymphoma and CLL:

- CT scans of chest, abdomen and pelvis (and neck if clinically indicated)
- Peripheral blood for flow cytometry (CLL and NHL only)
- Quantitative serum immunoglobulin
- Serum ß2 microglobulin
- Serum LDH
- Patients with CLL should have FISH probes for deletion of chromosome 13, 11q, trisomy 12, and p53 analysis.

Post-transplantation

MM (*Waldenstrom's Macroglobulinemia patients, same as below with no skeletal survey, or MRI):

- Quantitative serum immunoglobulin levels on day 80. Repeat at 6, 12, 18 and 24 months and then annually x 5 years post-transplant.
- Serum protein electrophoresis and immunofixation on day 80. Repeat at 6, 12, 18 and 24 months and then annually x 5 years.
- **All patients** will have twenty-four hour urine collection for protein, creatinine clearance, urine protein electrophoreis (UPEP) and immunofixation (IFX) at **12 months.** Patients with an abnormal UPEP/IFX pretransplant, will have additional twenty-four hour urine collection for protein, creatinine clearance, UPEP, and IFIX at day +80, then 6, 12, 18 and 24 months, and then annually x 5 years.
- Complete skeletal survey, including skull and long bones at 12 months and then annually x 5 years. MRI of skeleton at 12 months and then annually x 5 years.
- Serum β2 microglobulin at 6, 12, 18 and 24 months and then annually x 5 years.

NHL, HD and CLL:

- CT scans of chest, abdomen and pelvis (neck if clinically indicated) at day 56 if abnormal pretransplant and day 80 for all patients. Repeat at 6, 12, 18, and 24 months and then annually x 5 years post-transplant.
- Patients with CLL and NHL with peripheral blood involvement with lymphoma pretransplant: flow cytometry analysis on day 28, 56, 80. Repeat at 6, 12, 18, and 24 months and then annually x 5 years.
- For CLL patients, quantitative serum immunoglobulin levels on day 80. Repeat at 6, 12, 18 and 24 months and then annually x 5 years. If abnormal pre-transplant.

Appendix X: Potential Adverse Events Associated or Expected with Hematopoietic Cell Transplantation

1. Graft versus host disease. GVHD is a major toxicity associated with the infusion of allogeneic donor stem cells. GVHD may be acute or chronic and may affect multiple organ systems, including the skin, liver, and GI tract.

2. Opportunistic infections. including viral and fungal infections, can result in severe pulmonary, neurologic, hepatic and other organ dysfunction, and possible death.

3. Gastrointestinal toxicity. Nausea and vomiting can be anticipated during the entire course of ablative therapy. Mucositis and diarrhea should be expected. Prednisone can cause GI bleeding.

4. Cardiac toxicity. Cardiotoxicity (congestive heart failure, pericardial effusion, EKG changes) is uncommonly associated with the chemotherapy agents and TBI used in the regimen and these sequelae may prove lethal.

5. Pulmonary toxicity. Diffuse interstitial pneumonitis of unknown etiology and diffuse alveolar hemorrhage occurs with some regularity after BMT and interstitial fibrosis occurs much more rarely. Both are well-described complications of intensive chemotherapy and TBI regimens and may prove lethal.

6. Hepatic toxicity. Veno-occlusive disease of the liver is a common toxicity of high-dose chemoradiotherapy and may result in death. Cyclosporine may cause elevation of ALT/AST.

7. Renal dysfunction. Chemoradiotherapy may uncommonly cause renal dysfunction. More commonly, nephrotoxicity results from cyclosporine and generally responds to dose reduction. Rarely, idiopathic or calcineurin inhibitor-associated hemolytic-uremic syndrome may occur and may be progressive and fatal. A syndrome of moderate renal insufficiency and hemolysis has been seen 5-7 months post HSCT after intensive multi-agent conditioning plus TBI.

8. Hemorrhagic cystitis. manifested either as gross or microscopic hematuria, is a common toxicity after high-dose chemoradiotherapy, but usually associated with regimens that include cyclophosphamide. Hemorrhagic cystitis may predispose to a long-term increased risk of bladder cancer.

9. Central nervous system toxicity. Radiation and chemotherapy can cause CNS toxicity, including seizures, depressed mental status, or leukoencephalopathy. Calcineurin inhibitors can cause seizures or other CNS toxicity.

10. Marrow aplasia. Severe neutropenia, thrombocytopenia, and anemia, is expected to occur for a period of 7 to 42 days following infusion of marrow. Transfusion of platelets and red blood cells is expected as supportive care. Transfusion of blood products may be associated with acquisition of HIV or a hepatitis virus. Neutropenia may increase the risk for acquiring serious infection. Thrombocytopenia may increase the risk of life-threatening hemorrhage. Hemorrhagic or infectious complications during the expected period of aplasia may result in death.

11. Miscellaneous. Alopecia and sterility are expected complications of the program as a whole. Cataract development is possible after TBI and/or steroids. Deficiencies of growth hormone, thyroid hormone, and sex hormones are possible after TBI. Calcineurin inhibitors can cause transient gingival hyperplasia, tremor, seizure, hypertension, headache, dysesthesia and hirsutism. Steroid therapy can also contribute to fluid retention, easy bruising, hypertension, aseptic necrosis of bone and increased susceptibility to infection. MMF can cause spontaneous abortions and birth defects. Hospitalization during conditioning and recovery period is expected to be 5-9 weeks in duration.