A Reduced Intensity Conditioning Regimen and the Transplantation of Unrelated Donor Umbilical Cord Blood in Patients with Hematologic Malignancies.

THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Table of Contents

1.0 PROTOCOL SUMMARY AND SCHEMA

This is a phase 2 study of reduced intensity conditioning (RIC) and the transplantation of an unrelated donor umbilical cord blood (UCB) graft in patients with acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL), advanced myelodysplasia (MDS), chronic myelogenous leukemia (CML), other myeloproliferative disease or Non-Hodgkin's lymphoma unsuitable for high dose myeloablative conditioning. The aim is to obtain a preliminary estimate of disease-free survival at 1 year post-transplant.

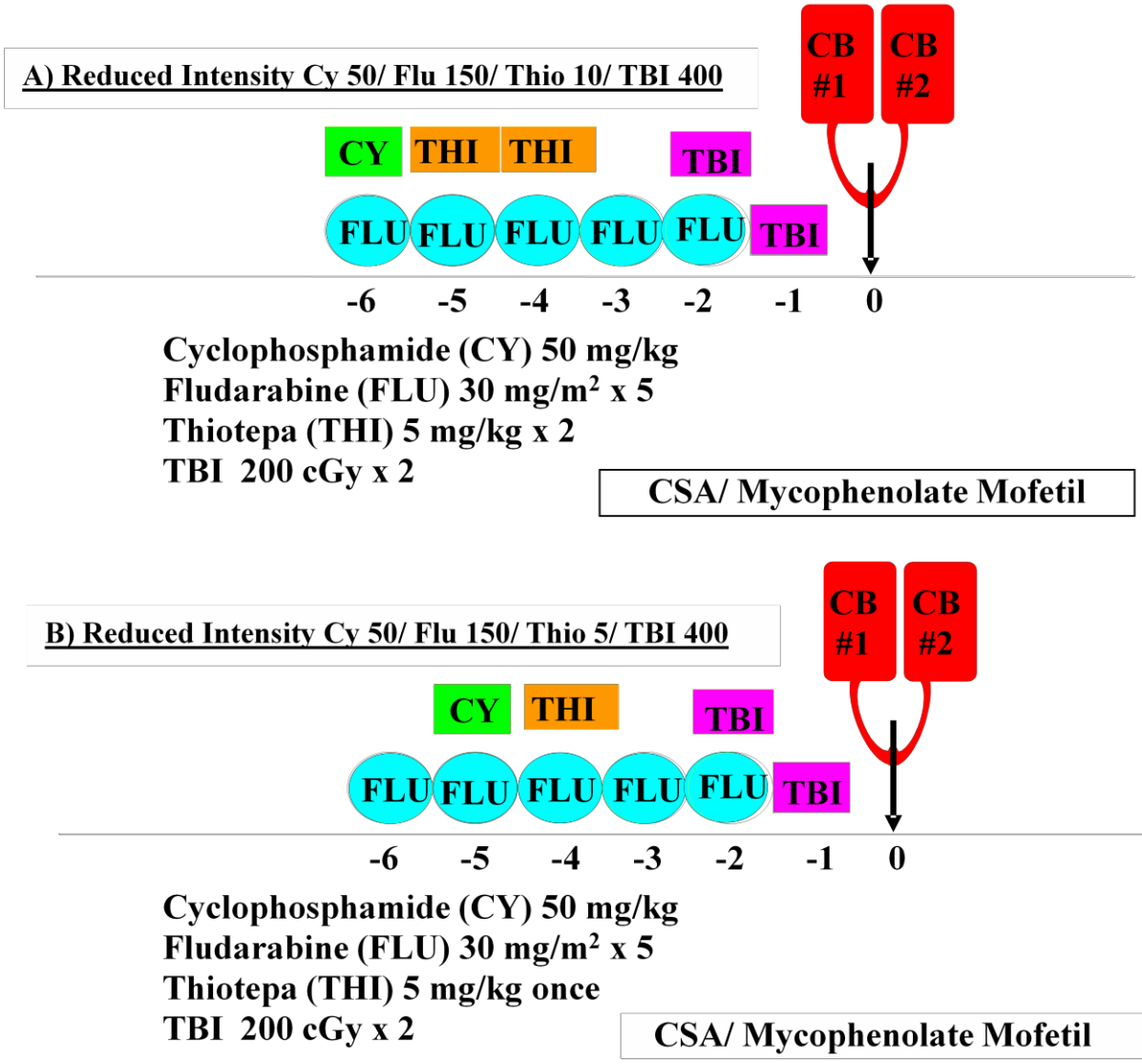
Transplant conditioning will consist of cyclophosphamide (Cy), fludarabine (Flu), thiotepa (Thio) and low dose total body irradiation (TBI) followed by the infusion of a double unit UCB graft. Cyclosporine (CSA) and mycophenolate mofetil (MMF) will be used for GVHD prophylaxis.

Candidates for this trial will include patients: 1) aged 18-70 years with AML, ALL, advanced MDS, CML, MPD or Non-Hodgkins or Hodgkins lymphoma at high risk of relapse for whom pre-transplant induction chemotherapy is possible; and 2) high dose myeloablative conditioning is not appropriate.

UCB will be used as the source of hematopoietic stem cells (HSCs). Grafts will consist of two partially HLA-matched UCB units to augment graft cell dose. Patients will be carefully monitored post-transplant for donor engraftment and count recovery, donor chimerism, incidence and severity of acute and chronic graft-versus-host disease (GVHD), serious infectious complications, transplant-related mortality (TRM), characteristics of immune recovery, as well as overall and disease-free survival. In addition, laboratory studies will be performed to investigate factors that may be associated with graft failure, GVHD and immune recovery.

Biostatistics will be based on a total of 80 patients undergoing UCBT. It is anticipated that the accrual will last 6 years. At the conclusion of the study, a preliminary estimate of the one-year disease-free survival after UCBT will be possible with a confidence of $\pm$ 0.13.

PROTOCOL SCHEMA



2.1 OBJECTIVES AND SCIENTIFIC AIMS

The primary aim of this study is to obtain a preliminary estimate of disease-free survival at 1 year post UCBT.

Secondary objectives include:

- the speed of neutrophil and platelet recovery post allograft;
- the incidence and speed of donor-derived engraftment and contribution of each UCB unit to engraftment;
- the incidence and severity of acute GVHD at 100 days;
- the incidence and severity of chronic GVHD at 1 year;
- immune recovery after transplant;

- the incidence of malignant relapse or disease progression at 1 and 2 years;
- the probabilities of overall survival at 1 and 2 years after UCBT;
- the probability of disease-free survival 2 years after UCBT;
- the correlation of engraftment and chimerism with pre-transplant measures of HLA antibodies
- graft characteristics potentially associated with engraftment.

3.0 BACKGROUND AND RATIONALE

Introduction

Acute leukemia comprises 2% of all malignancies in the United States. While some patients are cured with chemotherapy, patients with high-risk AML in 1st remission (e.g. AML secondary to MDS and/or high-risk cytogenetics), high-risk ALL in 1st remission (e.g. Philadelphia chromosome positive), and relapsed acute leukemia are not curable with standard therapy. Similarly, the only known potentially curative treatment for MDS is allogeneic transplant. However, widespread application of allogeneic transplant is limited by both a paucity of suitably matched and readily available donors and the inability of older patients, or those with co-morbidities, to withstand intensive conditioning. Treatment strategies for patients with these diseases with the potential for cure are needed. This protocol seeks to investigate the combined approach of UCB as a HSC source and reduced intensity conditioning (RIC) to resolve these limitations.

An additional high-risk AML group which will be eligible for this protocol is any AML patient age $\geq$ 55 years with intermediate-risk cytogenetics. The very poor prognosis of these adult AML patients at presentation has recently been highlighted by Appelbaum et al [3]. This retrospective analysis of 968 adults with AML on 5 recent Southwest Oncology Group trials investigated the impact of age upon outcome when treated with chemotherapy. Notably, the median DFS of patients (n = 246) aged 56-65 years was 7.4 months (6.5-8.8) and 8.3 months (6.3-10.2) in those aged 66-75 years. As shown in Figure 1, at 3 years after study entry the overall survival of all patients aged > 55 years with intermediate risk cytogenetics was < 20%. Those with high risk cytogenetics fared worse with all patients having a survival of less than 20% at 3 years, regardless of age.

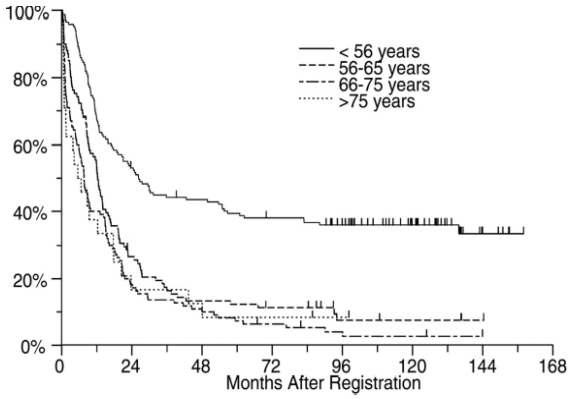


FIGURE 1A. Survival by age for AML patients with intermediate risk cytogenetics.

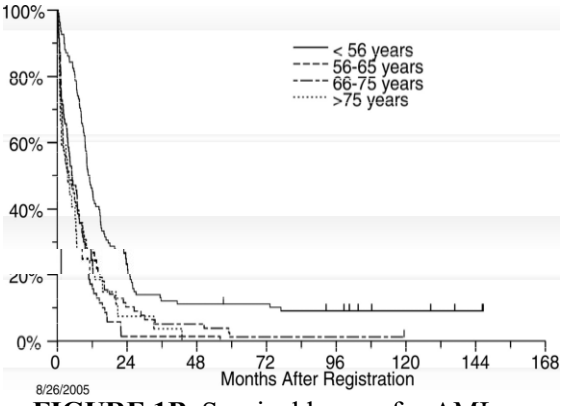


FIGURE 1B. Survival by age for AML patients with unfavorable risk cytogenetics.

These findings have been supported by Frohling et al who also found a 3 year survival of less than 20% for older patients with intermediate or high risk cytogenetics [4]. Novel therapies are needed for these patient populations. Therefore, this protocol will investigate RIC allograft for not only high-risk AML patients in CR1 by traditional criteria, but also any AML patients in CR1 with intermediate-risk cytogenetics age $\geq$ 55 years.

In addition to AML in older adults, patients with advanced MDS also have a poor prognosis. Cutler et al reported that survival is maximized if patients in intermediate 2 and high International Prognostic Scoring System groups are transplanted at diagnosis[5]. Patients with advanced MDS will therefore also be eligible for this protocol. Patients will require at least one cycle of prior induction chemotherapy or treatment with decitabine or azacitidine.

Patients with ALL will also be eligible. Both relapsed and poor-risk ALL in CR1 are accepted indications for allograft. Data from the GOELAMS group has demonstrated superior overall survival of allogeneic transplantation compared to high-dose consolidative therapy with autologous stem cell support in poor-risk disease [6]. The advantage of allogeneic transplant was also highlighted in the Plenary Session of the 2006 ASH conference presented by Rowe et al[7] in a large MRC/ECOG cooperative trial. This analysis demonstrated superior OS, EFS, and risks of relapse in intermediate-risk ALL patients receiving allograft versus standard post-remission chemotherapy. Moreover, despite lack of data regarding allogeneic transplantation for ALL patients $\geq$ 60 years, a prospective study of 519 patients in this demographic receiving standard induction chemotherapy resulted in median overall survival of 7 months supporting the investigation of alternative therapies [8].

Finally, other high risk patients with hematologic malignancies include patients with CML who have developed blast crisis or failed or are intolerant of standard therapy with tyrosine kinase inhibitors, and patients unable to tolerate the prolonged consolidation and maintenance chemotherapy regimens fair very poorly. These patients are also appropriate candidates for allograft as an alternative treatment strategy.

Clinical Results of Allotransplant in Acute Leukemia and MDS

RIC is being widely investigated as a potential means to extend the possibility of an allograft and the associated beneficial GVL effect to older patients or patients unsuitable for a high-dose regimen. This treatment approach is of particular interest in older leukemic patients in the age range of 50-70 years who are frequently not considered for allografting by referring physicians but have poor outcomes with conventional chemotherapy. Multiple studies have shown that such conditioning can be successfully used to ensure the engraftment of either sibling or unrelated volunteer donor HSC with low TRM even in patients who are older or extensively pre-treated[9-15]. These results demonstrate that RIC transplant in patients with acute leukemia, using predominantly sibling donors, is associated with low TRM despite relatively advanced age by allogeneic

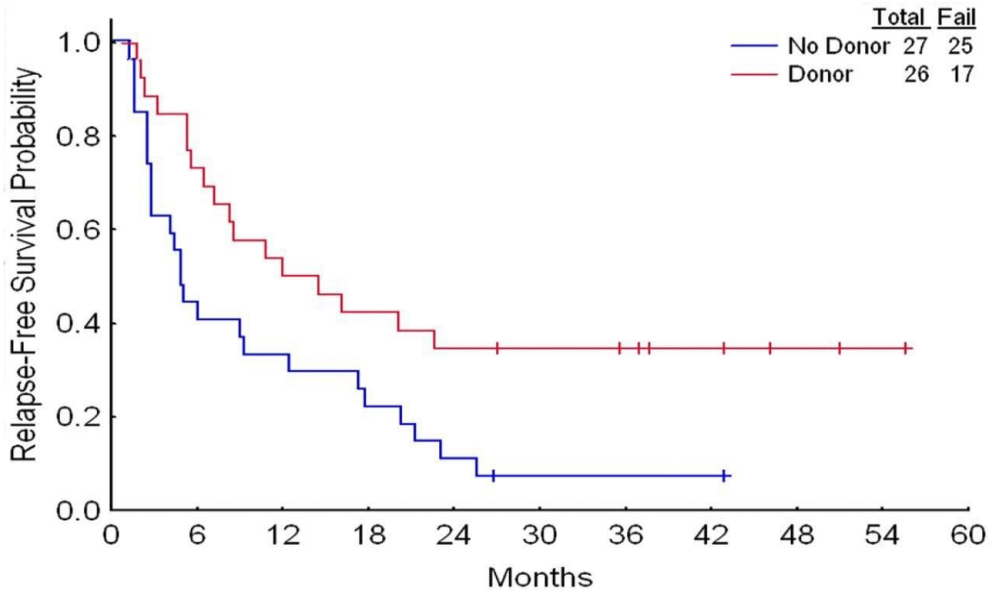


FIGURE 2. DFS after RI allograft vs chemotherapy in elderly AML/ MDS patients.

transplant standards and therefore warrants further investigation. A recent prospective study by Estey et al, as shown in Figure 2, supports an advantage of allogeneic transplant over chemotherapy in elderly AML and high risk MDS [16].

There are a number of limitations of this approach, however. Firstly, the intensity of the preparative regimen necessary to ensure disease control for these patients has not been fully defined. Also, non-myeloablative transplantation for patients with acute leukemia in relapse has not been successful. Further, for those with high risk disease, while TRM can be reduced after RIC as compared to higher dose conditioning, the risk of relapse is concomitantly increased. While some investigators, such as Flynn et al, have shown a comparable DFS after RIC to that after ablative conditioning in patients with AML and MDS[17], too much reduction in preparative intensity may be insufficient to ensure disease control. For example, in a study by de Lima et al while the least intense non-ablative conditioning was associated with improved TRM, a more intense, but still reduced intensity approach was associated with both improved donor engraftment and decreased relapse resulting in superior progression-free survival [18]. Therefore, in this protocol, a RIC regimen will be utilized in preference to a truly non-ablative regimen.

A further limitation of allogeneic transplantation is that many patients do not have a sibling or unrelated volunteer donor that is both suitably matched and available in the required time period. MSKCC data to date demonstrates that UCB extends transplant access to patients of ancestry other than northwestern Europe without suitable unrelated donors including racial and ethnic minorities (Table 1). In addition, UCB is available faster than unrelated donors [26]. Therefore, in this protocol UCB will be investigated as an alternative HSC.

Patient Ancestry	N	%
Northwest Europe	3	8
Eastern Europe	4	11
Southern Europe	5	13
Mix: Europe	7	18
Asian	6	16
African	6	16
Middle Eastern	1	3
Hispanic/ Latino	6	16
TOTAL	38	100

Table 1: Ancestry of UCB Transplant Recipients 10/05-11/07 (n = 38). The vast majority of patients received UCB if they did not have a suitably matched unrelated donor.

Unrelated Donor UCBT after Reduced Intensity Conditioning

Multiple reports have documented that UCB is capable of reconstituting hematopoiesis after intensive myeloablative therapy[1, 19-26]. Results of unrelated donor UCBT have demonstrated that banked UCB is rapidly available[27] and can successfully engraft the majority of small children with a relatively low incidence of acute and chronic GVHD despite HLA disparity[24]. This HSC source therefore permits an expansion of the donor pool and UCBT has become a standard alternative for the treatment of pediatric leukemia.

In contrast, adult UCBT has been limited by the low infused cell dose [18, 23, 25]. Therefore, for larger adolescents and adult patients undergoing UCBT, efforts have focused on improving engraftment and decreasing TRM. To address this problem the combined transplantation of two UCB units in a double unit graft has been investigated as a strategy to augment graft cell dose[26]. The initial University of Minnesota experience in 31 double unit myeloablative UCBT patients (median age 24 years; range 13-53) with hematologic malignancy was associated with sustained neutrophil engraftment in all evaluable patients (n = 29) at a median of 23 days (range 14-41). Interestingly, this engraftment was accounted for by one unit with neither nucleated cell dose nor HLA-match predicting unit predominance. The incidences of grade III-IV acute GVHD, chronic GVHD, and TRM were 24% (95% CI: 9-39) at 100 days, 32% (95%CI: 13-51) at 1 year, and 20% (95%CI: 6-34) at 6 months, respectively. At a median follow-up of 1.2 years (range 55 days-3.2 years), the Kaplan-Meier estimate of disease-free survival at 2 years was 60% (95%CI: 41-79) in all patients, and 68% (95%CI: 47-89) in patients (n = 23) transplanted in remission.

These results demonstrate that double unit UCBT can be performed safely in adults with improved engraftment and reduced TRM as compared to historical single unit controls. This strategy therefore extends access to allogeneic transplantation and introduces adult UCBT as a viable alternative to both matched and mismatched marrow transplantation. Interestingly, preliminary data also suggests that double unit UCBT may be associated with protection against relapse as compared to single unit UCBT.

Non-myeloablative UCBT has been investigated utilizing double unit grafts in those inappropriate for high dose conditioning in 110 high-risk adults (median age 51 years) with high-risk or advanced hematologic malignancies [1, 2]. Patients received cyclophosphamide 50 mg/kg, fludarabine 200 mg/m^2, and 200 cGy TBI (±anti-thymocyte globulin), with cyclosporine-A and mycophenolate mofetil, and either single (n = 17) or double (n = 93) 4-6/6 HLA-matched UCB units with a median total infused dose of 3.7 x 10^7 NC/kg. Neutrophil recovery occurred in 92% of patients at a median of 12 days (range 0-32). The cumulative incidence of sustained donor engraftment was 85% (95%CI: 77-92) overall. The cumulative incidence of grade II-IV acute GVHD was 59% (95%CI: 49-69) at day 100, and chronic GVHD was 23% (95%CI: 15-31) at 1 year, with a TRM of 19% (95%CI: 12-26) at day 180 and 26% (95%CI: 18-34) at 3 years. Notably, TRM was significantly reduced in patients > 45 years compared to those ≤ 45 years (15% vs 32%, P=.02) at 180 days. The probability of EFS was 38% (95%CI: 28-48) at 3 years.

Therefore, this approach has been associated with a high overall incidence of sustained engraftment and relatively low TRM in older or extensively pre-treated adults provided they have satisfactory fitness and reasonable progression-free survival in this high-risk patient population. Notably, the survival after non-ablative UCBT is comparable to that of sibling donor non-ablative allograft [29]. However, prior

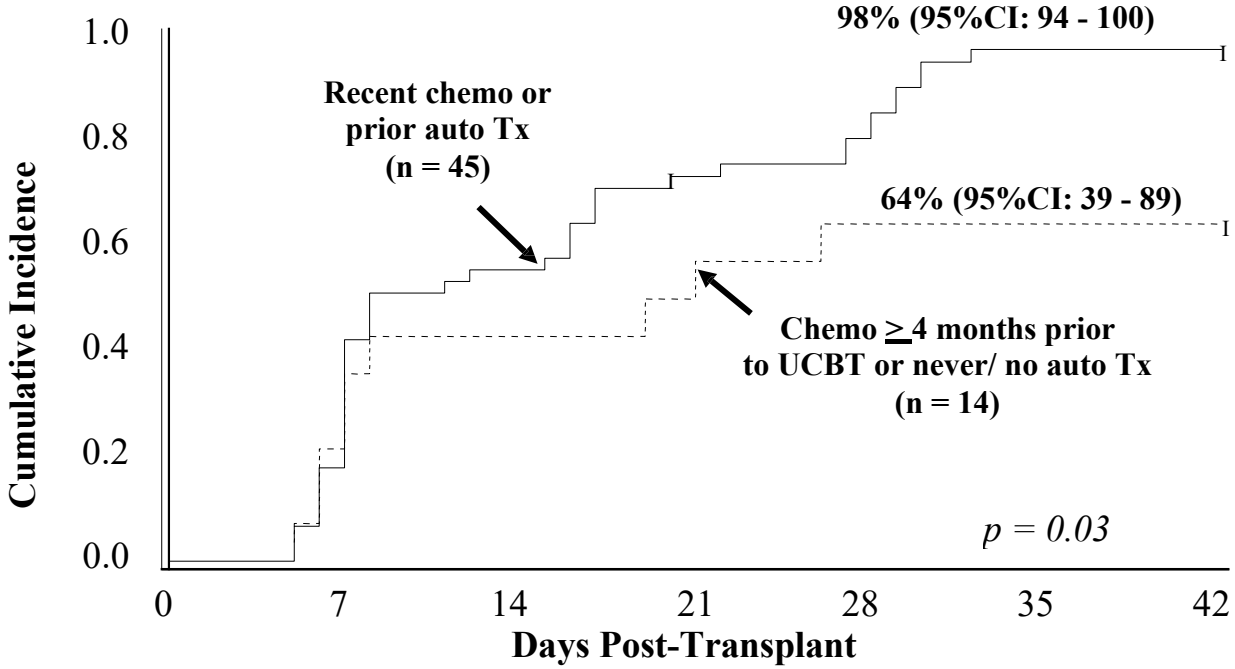


FIGURE 3. Sustained donor engraftment after non-ablative UCBT according to prior therapy (n = 59). University of Minnesota data, PI: J. Barker.

chemotherapy has been found to be an important factor in ensuring donor engraftment after non-myeloablative therapy. As seen in University of Minnesota data in Figure 3, patients with recent combination chemotherapy or a prior autologous transplant had a 98% cumulative incidence of sustained donor engraftment. This is in

comparison to only 64% sustained engraftment in patients without such prior therapy likely due to the ability of the latter group to reject their grafts.

This protocol will therefore: 1) dictate at least one cycle of prior chemotherapy (including decitabine or azacitidine for MDS or a tyrosine kinase inhibitor for CML); and, 2) utilize a RIC regimen rather than non-myeloablative conditioning. Combined, this approach should enhance both disease control and donor engraftment. However, to ameliorate potential organ toxicity in older patients >/= 60 years and those with significant comorbidities, a regimen with only 5 mg/kg thiotepa will be investigated for this patient population.

Because any patient receiving less than a fully ablative regiment is at increased risk of graft rejection, this protocol will also perform correlative laboratory studies to investigate whether pre-transplant T-cell function and/or HLA antibodies are associated with mixed donor chimerism or graft rejection. Blood of patients with myelodysplasia and chronic phase CML will be assayed pre-transplant in the Clinical Laboratory (Katherine Smith, PhD) to quantify T cell numbers (CD3+CD4+/CD8+) and T cell proliferative capacity as measured by PHA response. Additionally, HLA antibodies will be measured in all patients at the American Red Cross HLA Laboratory (Susan Hsu, PhD). Those patients with a positive screen for antibody(ies) against HLA Class I (A,B,C) and/or Class II (DRB1,DQ) loci will have the HLA specificity(ies) of the antibody(ies) determined in a semi-quantitative assay. Antibodies of most interest will be those directed against HLA loci exclusively present in the donor. Results of the T cell count and activity, and presence of HLA allo-antibodies (especially if against donor HLA loci) will be correlated with the risk of graft failure and donor chimerism measured at days 21 (BM), 28 and 60 (blood) post-transplant. In addition, correlative laboratory studies of double unit biology will be performed, and immune recovery and serum markers of GVHD will be assessed.

Summary

Select patients with high risk 1st remission or relapsed acute leukemia, advanced MDS, CML, or MPD may benefit from the GVL effect of allogeneic transplant. However, many patients with these diseases do not have a suitably matched related or unrelated donor and are not suitable candidates for conventional high-dose conditioning. UCBT with RIC is a valid alternative for these patients. Prior chemotherapy will be given to facilitate donor engraftment and optimize disease control. In addition, a reduced intensity rather than a truly non-myeloablative approach will be used to enhance both engraftment and disease control. Non-Hodgkins lymphoma patients, including those with chronic lymphocytic leukemia who are not suitable for either high dose ablative or a non-myeloablative regimen, will also be eligible. Stopping rules for TRM will optimize patient safety. Correlative laboratory studies will be performed to investigate double unit biology and immune recovery and GVHD post-transplant.

4.1 OVERVIEW OF STUDY DESIGN / INTERVENTION

4.2 Design

This is a phase 2 study to evaluate the disease-free survival after RIC UCBT, utilizing double unit grafts to augment graft cell dose, in patients with acute leukemia, advanced MDS, CML, MPD or Non-Hodgkins lymphoma (including CLL) not suitable for ablative conditioning. Pre-transplant chemotherapy will be required as part of transplant eligibility, both to contribute to recipient immune suppression and thus facilitate donor engraftment and to reduce disease burden. This should consist of induction (or re-induction) chemotherapy. Problems with engraftment or severe GVHD after UCBT and other adverse experiences will be monitored throughout the study by the MSKCC allogeneic BMT research data managers and reported to the Principal Investigator. Stopping rules are in place for excess toxicity as evidenced by TRM > 30% at day 100 post UCBT.

4.3 Intervention

Select patients with high risk 1st remission or relapsed acute leukemia, advanced MDS, CML or Non-Hodgkins lymphoma may benefit from the GVL effect of allogeneic transplant. However, many patients with these diseases do not have a suitably matched related or unrelated donor and are not suitable candidates for conventional high-dose conditioning. UCBT with RIC is a valid alternative for these patients. Prior chemotherapy will be given to facilitate donor engraftment and optimize disease control. In addition, a reduced intensity rather than a truly non-myeloablative approach will be used to enhance both engraftment and disease control. Stopping rules for TRM will optimize patient safety. Correlative laboratory studies will be performed to investigate both pre-transplant patient factors associated with graft rejection or mixed chimerism, as well as double unit biology, immune recovery, and GVHD post-transplant.

Candidates for this trial will include patients: 1) aged 18-70 years with AML, ALL, advanced MDS, CML, MPD or Non-Hodgkins lymphoma who are at a high risk of relapse for whom pre-transplant induction chemotherapy is possible; and 2) myeloablative conditioning is not appropriate.

Transplant conditioning will consist of cyclophosphamide (Cy), fludarabine (Flu), thiotepa (Thio) and low dose total body irradiation (TBI) followed by the infusion of a double unit UCB graft. A less intense regimen will be used in patients >/= 60 years and those with significant comorbidities. Cyclosporine (CSA) and mycophenolate mofetil (MMF) will be used for GVHD prophylaxis. UCB will be used as the source of hematopoietic stem cells (HSCs). Grafts will consist of two partially HLA-matched UCB units to augment graft cell dose.

5.1 THERAPEUTIC/ DIAGNOSTIC AGENTS

5.2 Cyclophosphamide (Cytoxan®, Neosar®)

Supplied as: 200 mg, 500 mg, 2000 mg vials

Reconstitution directions: add sterile water for injection to yield a final concentration of 20 mg/ml.

Storage and stability:

1. Store vials at room temperature.
2. Refrigerated: prepare infusion in d5w, stable for 28 days.
3. **Room temperature: prepare infusion in d5w: stable for 48 hours**

Preparation:

1. Standard IV fluid: d5w.
2. Final concentration range up to: 20mg/ml.
3. IV piggyback volume: for doses < 1200mg/m^2, infuse in 25cc d5w; for doses> 1200mg, infuse as straight drug.

Clinical considerations:

- Hemorrhagic cystitis is a common side-effect but can be reduced by administering drug early in the day, high volume fluids, and encouraging patient to empty their bladder frequently.
- Drug may cause nasal congestion which can be improved by slowing the infusion.
- Must monitor electrolytes for SIADH.
- Hydration: as per MSKCC guidelines.
- Emetic potential: high and delayed.

- Supportive medications: anti-emetics as per MSKCC guidelines
- Toxicities: see Section 11.0.
- Incompatibilities: do not administer with other drugs.

5.3 Fludarabine phosphate (Fludara®)

Supplied as: 50mg vial

Reconstitution directions: add 2ml of sterile water for injection to a 50mg vial; yields a final concentration of 25 mg/ml.

Storage and stability:

1. Store vials under refrigeration.
2. Refrigerated: prepare infusion in d5w; stable for 16 days.
3. **Room temperature: prepare infusion in d5w; stable for 16 days.**

Preparation:

1. Standard iv fluid: d5w.
2. Final infusion concentration range: up to 10mg/ml.
3. IV piggyback volume: 50 cc.

Clinical considerations:

- Hydration: 500 cc saline. May require higher fluid rate if at risk for tumor lysis.
- Emetic potential: low.
- Supportive medications: none.
- Toxicities: see Section 11.0.
- Incompatibilities: acyclovir, amphotericin B, chlorpromazine, daunorubicin, ganciclovir, hydroxyzine, miconazole, prochlorperazine.

5.4 Thiotepa (Thioplex®)

Supplied as: 15 mg, 30 mg, powder for reconstitution

Reconstitution directions: Reconstitute each vial to 10 mg/mL. Solutions for infusion should be diluted to a concentration ≥5 mg/mL in 5% dextrose or 1, 3, or 5 mg/mL in 0.9% sodium chloride injection. Filter through a 0.22 micron filter prior to administration.

Storage and stability:

1. Store intact vials under refrigeration (2°C to 8°C). Protect from light.
2. Reconstituted solutions (10 mg/mL) are stable for up to 28 days under refrigeration (4°C to 8°C) or 7 days at room temperature (25°C).
3. Solutions for infusion in D_5W (≥5 mg/mL) are stable for 14 days under refrigeration (4°C) or 3 days at room temperature (23°C).
4. Solutions for infusion in NS (1, 3, or 5 mg/mL) are stable for 48 hours under refrigeration (4°C to 8°C) or 24 hours at room temperature (25°C). Solutions in NS at a concentration ≤0.5 mg/mL are stable for <1 hour.

Clinical considerations:

- Hydration: NA
- Emetic potential: low.
- Supportive medications: none.
- Toxicities: see Section 11.0.
- Incompatibilities: cisplatin, filgrastim (G-CSF), vinorelbine

5.5 Total Body Irradiation (TBI)

Treatment planning begins with a simulation. Patients will receive a total dose of 400 cGy on day -2 and day -1 as 2 fractions (200 cGy x 2). Patients receiving total body irradiation (TBI) are treated in a standing position, and the treatment takes about 20 to 30 minutes. Toxicities are outlined in Section 11.0.

5.6 Cyclosporine (Sandimmune)

Supplied as: 50 mg/ml; 5 ml ampule (protect from light)

Reconstitution: N/A

Indications: Immunosuppressant used in the prevention of graft-versus-host-disease (GVHD) following allogeneic bone marrow transplantation.

Storage and Stability: Prepare in a glass bottle only. Stability is 72 hours under refrigeration or at room temperature.

Preparation:

1. Dilute in D5W or NS to make a 2.5 mg/ ml solution.
2. Infuse slowly over approximately 1-4 hours (intermittent infusion) or 24 hours for continuous infusion.

Clinical Considerations:

- Patients should be under close observation for possible allergic manifestations including facial flushing, respiratory distress, with dyspnea and wheezing, blood pressure changes and tachycardia.
- Prior to infusion solution should be inspected visually for particulate matter and discoloration.
- Other nephrotoxic agents will increase the risk of nephrotoxicity (amphotericin B, aminoglycosides, and acyclovir).
- Plasma concentrations of cyclosporine may be affected by the following drugs:
- Increased cyclosporine levels: ketoconazole, erythromycin, cimetidine, calcium channel blockers, fluconazole, itraconazole, norfloxacin, imipenem/ cisplatin
- Decreased cyclosporine levels: rifampin, phenytoin, phenobarbital, imipenem/ cisplatin.
- The IV to oral dose conversion is 1:3. The target serum level of 200- 400 is desirable; 800 is considered toxic.
- Renal and hepatic parameters should be monitored routinely with dosage adjustments in the case of serum creatinine or LFT elevations.
- Toxicities: see section 11.0
- Incompatibilities: Do not co-administer with any drug.

5.7 Mycophenolate Mofetil (CellCept®)

Supplied as: 500 mg vial of powder for reconstitution.

Reconstitution: reconstitute each 500 mg vial with 14 ml of D5W only. Gently shake the vial to dissolve the drug. The vial will contain 500 mg of mycophenolate in approximately 15 ml.

Storage and Stability: Store at 15 -30°C. Drug compatible with D5W only. A final concentration of 6mg/ ml must be achieved prior to administration. Reconstituted vials and IV preparations are stable for up to 4 hours after preparation.

Preparation:

1. Reconstitute each 500 mg vial with 14 ml of D5W.
2. Gently shake the vial to dissolve the drug.
3. Drug must be further diluted to a final concentration of 6 mg/ml. A 1000 mg dose should be placed in 140 ml of D5W.
4. Mycophenolate Mofetil vials are stable for 4 hours at room temperature after reconstitution.
5. Doses of mycophenolate may begin infusion into the patient up to 4 hours after initial reconstitution of the vials.

Clinical Considerations:

- Administer only with D5W, over at least 2 hours. Mycophenolate is mutagenic, carcinogenic, and teratogenic. Precautions must be taken when handling this product. If medication comes in contact with skin, wash thoroughly with soap and water.
- Toxicities: see section 11.0
- Incompatibilities: Only compatible with D5W.

5.8 Filgrastim/ Granulocyte-Colony Stimulating Factor (Neupogen®)

Supplied as: 300 mcg/ml; 1 ml vial (300 mcg) and 1.6 ml vial (480 mcg); 300 mcg/0.5 ml pre-filled syringe; 480 mcg/0.8 ml pre-filled syringe.

Storage and Stability: Store in a refrigerator (2-8°C). Do not freeze. If inadvertently the filgrastim is exposed to freezing temperatures for up to 24 hours, it may be thawed and refrigerated for use. Avoid shaking. Filgrastim may be allowed to reach room temperature for 24 hours prior to use.

Preparation:

1. For IV infusion, dilute filgrastim in 25-50 ml D5W.
2. The minimum concentration must not be less than 5 mcg/ml.
3. If the final concentration of filgrastim in solution is between 5-15 mcg/ml, albumin 2 mg/ml must be added to the solution prior to addition of the drug.
4. Stability (IV) once diluted in 25-50 ml of D5W, filgrastim is stable for 7 days.
5. Stability (plastic syringe) filgrastim is stable for two weeks in BD 1 ml plastic TB syringes at 2-8°C.
6. For the prevention/treatment of chemotherapy induced neutropenia, the dose of filgrastim is standardized per body weight: ≤ 60 kg = 300 mcg daily subcutaneously; > 60 kg = 480 mcg subcutaneously daily.

Clinical Considerations:

- If being administered as an intermittent IV infusion, it should be administered via an infusion control device and administered over a 15- 30 minute period.
- Incompatibilities: The drug may precipitate in the presence of Normal Saline. Do not mix with any other drugs.

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

Eligibility for the protocol and timing of transplant admission should be determined by consultation with the physicians of the Adult Allogeneic Bone Marrow Transplant Service as soon as possible during induction or re-induction chemotherapy. A UCB graft will be secured during chemotherapy. At least one cycle of chemotherapy or disease active agent is necessary for protocol eligibility. More than one cycle of chemotherapy (e.g. induction and a single cycle of consolidation) may be necessary to ensure disease control while securing the allograft. Once chemotherapy is complete, pre-allograft work-up will be performed by the Allogeneic BMT Service as an outpatient. Eligible patients will be consented by the Allo BMT service and then admitted to the Adult Bone Marrow Transplant Unit for UCBT.

6.2 Subject Inclusion Criteria

At least one cycle of induction or re-induction chemotherapy or lymphoma chemotherapy or azacitidine or decitabine or tyrosine kinase inhibitor.

Age and Donor Status:

- Patients aged 18-70 years at initial referral with no available and suitably matched related or unrelated donor.

Diagnosis including:

- Acute myelogenous leukemia (AML):
  - Complete first remission (CR1) at high risk for relapse such as:
    - Known prior diagnosis of myelodysplasia (MDS) or myeloproliferative disorder;
    - Therapy related AML;
    - White cell count at presentation > 100,000;
    - Presence of extramedullary leukemia at diagnosis;
    - Any unfavorable subtype by FAB or WHO classification;
    - High-risk cytogenetics (e.g. those associated with MDS, abnormalities of 5, 7, 8, Philadelphia chromosome, complex karyotype) or high risk molecular abnormalities;
    - Requirement for 2 or more inductions to achieve CR1.
    - Any patient with newly diagnosed AML with intermediate risk cytogenetics.
    - Any patient unable to tolerate consolidation chemotherapy as would have been deemed appropriate by the treating physician.
  - Complete second remission (CR2).

- Acute lymphoblastic leukemia (ALL):
  - Complete first remission (CR1) at high risk for relapse such as:
    - White cell count at presentation > 30,000 for B-cell lineage and > 100,000 for T-cell lineage;
    - Presence of a high-risk cytogenetic abnormality such as t(9;22), t(1;19), t(4;11) or other MLL rearrangements (11q23) or other high-risk molecular abnormality;
    - Failure to achieve complete remission after four weeks of induction therapy;

- Any patient with newly diagnosed ALL ≥ 50 years-old;
- Any patient unable to tolerate consolidation and/or maintenance chemotherapy as would have been deemed appropriate by the treating physician.

- Complete second remission (CR2).

- Other acute leukemias that are ambiguous lineage or of other types e.g. blastic plasmacytoid dendritic cell neoplasm in CR1 or CR2.

- Myelodysplastic Syndrome (MDS):
  - Intermediate-1 International Prognostic Scoring System (IPSS) score with poor risk cytogenetics as defined by IPSS.
  - Intermediate- 2 or High International Prognostic Scoring System (IPSS) score.
  - MDS/ myeloproliferative disorder overlap syndromes.
  - Any score with life threatening cytopenia(s), including red cell or platelet transfusion dependence.
  - Receipt of at least one cycle of cytotoxic chemotherapy, azacitidine or decitabine.
  - MDS patients must have ≤ 5% bone marrow myeloblasts and ANC ≥ 0.2 (growth factor supported if necessary) at transplant work-up.

- Myeloproliferative Disorder (MPD)
  - Life-threatening cytopenia(s), and/or red blood cell or platelet transfusion dependence
  - Patients with aplasia
  - Patients with excess blasts less than or equal to 10% blasts in the bone marrow at work-up.

- Chronic myelogenous leukemia (CML) patients who have failed or are intolerant of tyrosine kinase inhibitors or patients with other myeloproliferative diseases who are high risk and the intent of therapy is cure.

- Any Non-Hodgkins lymphoma (including chronic lymphocytic leukemia) or Hodgkin's lymphoma at high-risk of relapse
  - Eligible patients with DLC NHL will:
    - have relapsed disease following initial therapy but failed to mobilize or had bone marrow involvement and therefore are not suitable for an autologous transplant OR
    - have failed an autologous transplant and be in CR after salvage chemotherapy.
  - Eligible patients with transformed indolent NHL/CLL will:
    - have CR/PR of the large cell component of their disease after either salvage chemotherapy or an autologous transplant.
  - Eligible patients with mantle cell NHL will:
    - be high-risk as such as p53 positivity and be in 1st CR/PR after initial therapy OR
    - have relapsed disease following initial therapy and be in 2nd or 3rd CR/PR after salvage chemotherapy.
  - Eligible patients with indolent B cell NHL (such as, but not limited to, follicular, small cell or marginal zone NHL) or CLL will have 2nd or subsequent progression (pre-allograft cytoreduction necessary but CR/PR not required).
  - Eligible patients with HL will be without progression of disease (POD) after salvage chemotherapy.

Timing of UCBT:

- Admission for UCBT must be within an acceptable time period after the pre-allograft chemotherapy.

Organ Function and Performance Status Criteria:

- Karnofsky score $\geq$ 70 %.
- ***calculated*** creatinine clearance $\geq$ 60 ml/min.
- bilirubin < 1.5 mg/dL, ALT $\leq$ 3 x upper limit of normal unless benign congenital hyperbilirubinemia.
- pulmonary function (spirometry and corrected DLCO) $\geq$ 50% predicted.
- left ventricular ejection fraction $\geq$ 50%.
- albumin $\geq$ 3.0.

Graft Criteria:

- 2 UCB units selected according to current MSKCC unit selection algorithm. High resolution 8 allele HLA typing will be performed. Unit selection will occur based on 8 allele HLA-match and CD34+ dose.
- In addition, each unit will have a cryopreserved dose of at least 1.5 x 10^7 total nucleated cells/recipient body weight (TNC/kg).
- Units with attached segments for confirmatory typing will be given preference.

6.3 Subject Exclusion Criteria

- Diagnosis: acute leukemia in morphologic relapse or with morphologic persistent disease (cytogenetic or molecular persistence/relapse in morphologic CR are eligible); MDS or CML or other myeloproliferative disorder with > 5% blasts; Aggressive lymphoma or HL with POD after salvage chemotherapy.
- Two prior stem cell transplants of any kind.
- One prior autologous stem cell transplant within the preceding 12 months.
- One prior allogeneic stem cell transplant within the preceding 24 months.
- Prior radiation therapy with 400cGy or more of TBI.
- Active and uncontrolled infection at time of transplantation.
- HIV infection.
- Seropositivity for HTLV-1.
- Inadequate performance status/ organ function.
- Pregnancy or breast feeding.
- Patient or guardian unable to give informed consent or unable to comply with the treatment protocol including appropriate supportive care, follow-up, and research tests.

7.0 RECRUITMENT PLAN

Patients who fulfill the eligibility criteria as listed in Section 6.0 will be recruited for this study by an Attending Physician of the Adult Allogeneic BMT service. Informed consent will be obtained by one of the participating investigators authorized to obtain consent. Confirmation of patient eligibility will be done via the medical Clinical Trials Office.

This protocol will take due notice of NIH/ADAMHA policies concerning inclusion of women and minorities in clinical research populations. We expect that the study population will be enriched for patients of ancestry other than northwestern European within the limits of being able to identify a suitable UCB graft. Pregnant women are excluded from participation in this study.

8.1 PRETREATMENT EVALUATION

8.2 The following tests must be performed.

1. **Standard clinical pretreatment evaluations**
   The following tests must be performed as per Adult BMT standard of care:

   a. Within 30 days prior to admission:
      i. Complete history, review of systems, physical exam (including performance status).
      ii. CBC with differential, comprehensive metabolic panel including albumin, LDH, PT/ PTT.
      iii. Pregnancy test for females of childbearing age (serum or urine HCG) to be performed within 2 weeks (15 days) of planned treatment. This is test is not required in exempt patients as defined below:
         1. Bilateral Oophorectomy
         2. Bilateral Salpingectomy
         3. Bilateral Salpingectomy-Oophorectomy
         4. Hysterectomy
         5. Menopause (no menses ≥ 1 year prior to treatment or after completion of all treatment)
         6. Surgical Sterilization (i.e., tubal ligation or blockage)

   b. Within 45 days prior to admission:
      i. Bone marrow aspirate (trephine core if clinically required) for morphology, and special studies (surface markers, cytogenetics, FISH and molecular studies) as warranted for documentation of disease status and bone marrow morphology.

   c. Prior to admission standard workup studies per Adult BMT Program including:
      i. Spinal or intra-Ommaya tap for evaluation of evidence of CNS leukemia as appropriate if patients with acute leukemia are at risk for CNS disease. Red blood cell type and screen (ABO blood type)..
      ii. EKG.
      iii. Echocardiogram or MUGA scan with measurement of left ventricular ejection fraction.
      iv. Radiographic studies if clinically indicated for diagnosis.
      v. Chest CT scan without contrast to exclude occult fungal infection prior to transplant (unless CT with contrast required for disease assessment eg NHL).
      vi. Pulmonary function testing including DLCO. Clinical and radiological assessment can substituted in small children.

vii. Testing for CMV (IgG and IgM), HIV-1/2, HTLV-1/2, toxoplasmosis, Hepatitis B (surface antigen, surface antibody), Hepatitis C antibody, Herpes Simplex, Herpes Zoster, Epstein Barr Virus, and syphilis.
viii. Peripheral blood from the patient should be submitted to the Diagnostic Molecular Pathology (DMP) Laboratory for future chimerism studies.
ix. HLA antibodies to the American Red Cross.

Note if prior serology testing has documented sero-positivity for an infection such as CMV or EBV it does not need to be repeated during the pre-transplant workup.

2. Pretreatment Protocol Research Tests

a. Prior to conditioning:
   i. Research labs: approximately 30cc (green and red top tubes) should be sent to the research laboratories as part of correlative laboratory studies.

9.1 TREATMENT/ INTERVENTION PLAN

Eligible patients will require a tunneled triple lumen central venous catheter and will be admitted to the Adult Bone Marrow Transplant Unit for UCBT. Patients will be maintained in reverse isolation as per the allogeneic BMT clinical care guidelines.

9.2 A) Conditioning Prior to UCBT if < 60 Years and Comorbidity Score (HCT-CI) of 0-4

Day	Treatment
-7	Admit and line placement
-6	Fludarabine 30 mg/m^2 IV Cyclophosphamide 50 mg/kg IV
-5	Fludarabine 30 mg/m^2 IV Thiotepa 5 mg/kg IV
-4	Fludarabine 30 mg/m^2 IV Thiotepa 5mg/kg IV
-3	Fludarabine 30 mg/m^2 IV Start MMF and CSA IV
-2	Fludarabine 30 mg/m^2 IV, TBI 200 cGy
-1	TBI 200 cGy
0	UCBT

Cyclophosphamide 50 mg/kg/dose x 1 IV day -6 (1 dose)
Fludarabine 30 mg/m^2/dose x 5 IV days -6 to -2 (5 doses)
Thiotepa 5 mg/kg/dose x 2 IV days -5 to -4 (2 doses)
TBI 200 cGy/dose x 2 days -2 to -1 (2 doses).

- Fludarabine 30 mg/m²/day should be administered as per MSKCC guidelines in the morning over approximately 30-60 minutes on days -6 to -2. Fludarabine dose should be calculated based upon adjusted body weight if the patient is $\geq$ 125% ideal body weight.

- Cyclophosphamide:
  - should be administered as per MSKCC guidelines on day -6 after the fludarabine is complete.

- Cyclophosphamide dose should be adjusted if patient is ≥ 125% ideal body weight (IBW) and should be calculated on adjusted body weight per MSKCC standard of care guidelines.
- Fluids should be per MSKCC standard of care with diuretics as required to maintain fluid balance.

- Thiotepa will be given as a 4 hour infusion on days -5 and -4. Thiotepa dose will be calculated based upon adjusted body weight if the patient is ≥ 125% ideal body weight.
- Total Body Irradiation: 200 cGy per dose on days -2 and -1 (2 doses). Both doses of TBI may be given on day -1 if necessary because of scheduling conflicts.

B) Conditioning Prior to UCBT if 60-70 years or patients < 60 years not suitable for conditioning of higher intensity including patients with HCT-CI score of 5 or higher.

In this regimen thiotepa dose will be reduced to 5 mg/kg:

Day	Treatment
-7 or -6	Admit and line placement
-6	Fludarabine 30 mg/m^2 IV
-5	Fludarabine 30 mg/m^2 IV Cyclophosphamide 50 mg/kg IV
-4	Fludarabine 30 mg/m^2 IV Thiotepa 5 mg/kg IV
-3	Fludarabine 30 mg/m^2 IV Start MMF and CSA IV
-2	Fludarabine 30 mg/m^2 IV, TBI 200 cGy
-1	TBI 200 cGy
0	UCBT

- Fludarabine: 30 mg/m²/day should be administered as per MSKCC guidelines in the morning over approximately 30-60 minutes on days -6 to -2 (5 doses). Fludarabine dose should be calculated based upon adjusted body weight if the patient is ≥ 125% ideal body weight.
- Cyclophosphamide: 50 mg/kg IV will be given for one dose. It should be administered as per MSKCC guidelines on day -5 after the fludarabine is complete. Cyclophosphamide dose should be adjusted if patient is ≥ 125% ideal body weight (IBW) and should be calculated on adjusted body weight per MSKCC standard of care guidelines. Fluids should be per MSKCC standard of care with diuretics as required to maintain fluid balance.
- Thiotepa: 5 mg/kg/day IV given as a 4 hour infusion on day -4. Thiotepa dose will be calculated based upon adjusted body weight if the patient is ≥ 125% ideal body weight.
- Total Body Irradiation: 200 cGy per dose on days -2 and -1 (2 doses).

9.3 GVHD prophylaxis

All patients will receive GVHD prophylaxis with 2 drugs as follows:

Cyclosporine

- Cyclosporine A (CSA) will be given per current MSKCC guidelines.
- It will begin on day -3 intravenously in the AM to achieve therapeutic levels per MSKCC guidelines.
- Initial dosing will be per the MSKCC guidelines of 3 mg/kg per dose (adjusted weight in the setting of marked obesity) starting day -3 and dose adjustments should be made on the basis of toxicity and sub- or supra-therapeutic CSA levels.
- Once the patient can tolerate oral medications, CSA can be converted to an oral form.
- In case of major CSA toxicity (e.g. CNS neurotoxicity documented by MRI), CSA should be discontinued. Patients may be re-challenged when clinically appropriate and alternative immune suppression should be substituted per MSKCC guidelines.
- Patients unable to tolerate CSA due to renal impairment should also be considered for an alternative immunosuppressant in addition to mycophenolate mofetil as per MSKCC guidelines.
- Standard patients will receive CSA for approximately 5-6 months in the absence of ongoing GVHD requiring systemic immune suppression. If no history or evidence of GVHD, CSA may be tapered with monitoring for GVHD with the aim to be off immunosuppression by approximately 8-9 months after transplant.
- In patients intolerant of CSA due to renal impairment or other toxicity CSA can be tapered before MMF. This is a reverse taper (see guidelines).
- For patients with GVHD, CSA may be continued for longer time periods according to standard of care guidelines
- If disease progression or persistence occurs, or the patient is considered to be at very high risk of relapse, early taper or cessation of CSA can be considered with close observation for GVHD.

Mycophenolate Mofetil

- Mycophenolate mofetil (MMF) will be given per current MSKCC MMF guidelines. It should begin on day -3 intravenously in the AM. Standard dose for adults is 15 mg per kg per dose IV q8 hours-see detailed dosing instructions in the
- Obtain therapeutic trough levels as per MSKCC guidelines.
- In preparation for discharge, switch to oral route (CellCept or generic mycophenolate mofetil). For oral conversion round to tablet size. If possible ensure both tablet strengths are given to patient to permit easy taper in clinic. On Pediatric Service can use liquid suspension. Avoid suspension on Adult Service.
- No dose adjustments for renal or liver disease are needed routinely unless severe organ dysfunction.
- If patient is $\geq$ +28 days and without neutrophil engraftment, consideration can be made to dose reduce dosing after discussion with PI or co-PI.
- If no evidence of GVHD, MMF can be tapered at approximately 60-100 days post-transplant. Taper at approximately 10-20% decrements. The aim to be off the drug by approximately 5-6 months. Earlier tapers can be considered if myelosuppression or high relapse risk with very close monitoring for GVHD. Abrupt reductions or cessation should be avoided due to GVHD risk.
- Patients who are intolerant of MMF due to myelosuppression may require earlier taper at the treating physician's discretion. Do not abruptly stop the drug unless life-threatening toxicity is suspected.

- If the patient is intolerant of CSA, MMF taper may be delayed i.e. do a reverse taper where CSA tapered first (see above).
- If the patient has acute GVHD requiring systemic therapy, MMF should only be tapered if control of GVHD has been obtained

9.4 UCB Thaw and Administration

- Units will be thawed by and released from the Cytotherapy Laboratory according to current standards of practice (SOPs) and release criteria. As per standard practice, ABO blood group, total nucleated cells (TNC), CD34+ and CD3+ cell number and viability, sterility and colony-forming units (CFU) will be measured post-thaw.
- If cell dose permits ($\leq$ 1% of the post-thaw TNC of each unit) will be used for laboratory research studies (see Section 10.5).
- Units should be administered promptly upon arrival to the patient care unit by IV infusion by the nursing staff under supervision of a BMT attending physician. UCB infusion nursing guidelines should be followed.
- Units should be given consecutively each over approximately 30-45 minutes, but can be slowed for serious infusion reactions as appropriate.
- Pre-medication should be as per current cord blood infusion guidelines.
- IV hydration per standard of care.

Following infusion the bag and tubing from each UCB unit must be submitted to the Microbiology Laboratory. Specimen from each UCB unit for Diagnostic Molecular Pathology will be forwarded by the personnel in the Cytotherapy Laboratory.

9.5 Growth Factor (G-CSF) after UCBT

G-CSF 5 mcg/kg/day IV/SQ (dose rounded to vial size to a maximum of 480 mcg) will be given to all patients post UCBT as from day +7 until ANC recovery. In the case of slow count recovery, consult PI and follow MSKCC guidelines.

10.1 EVALUATION DURING UCBT

10.2 Prophylaxis against Infection

Patients will be treated according to the allogeneic BMT standard of care guidelines and will be given prophylaxis against 1) Bacteria during neutropenic period 2) Pneumocystis carinii, 3) Herpes simplex and Herpes Zoster, and 4) fungal infections. Sero-positive patients will be closely monitored for activation of CMV and CMV viremia will be treated according to the BMT guidelines.

10.3 Transfusions

Following initiation of the pre-transplant cytoreduction, all blood products for transfusion (with the exception of the stem cell graft) will be irradiated as per MSKCC guidelines.

10.4 Prophylaxis Against Menstrual Bleeding

Post-pubertal females will be considered for hormonal therapy to suppress menses unless a specific contra-indication to estrogen exists.

10.5 Nutritional Support

Physicians will monitor nutritional status, and high-calorie supplementation and vitamin supplements will be administered as clinically indicated per standard practice.

10.6 Correlative Laboratory Studies

Pre-transplant Assays

- Anti-HLA antibodies: An immunofluorescence-microarray based technique, performed by the American Red Cross laboratories, will be used to screen patients' serum pre-transplant for specific anti-HLA-A, B, C, DRB1, and DQ antibodies (all patients).

Double Unit Biology Studies

Laboratory research studies will be performed using a maximum of ≤1% of each unit on the day of thaw investigating the determinants of (or factors associated with) unit predominance in patient engraftment. The correlative studies will include:

- Characterization of the composition of each unit by flow cytometry (Clinical Laboratory, Supervisor Katherine Smith).

Additional Studies may include:

- Analysis of the Killer Ig-like receptor (KIR) genotype to assess if NK alloreactive cells are involved in unit predominance (Dr Katherine Hsu's Laboratory).

As a maximum of 1% of each unit will be used for research, these studies may be limited by the number of cells available. Therefore, not all studies may be performed on every double unit pair and the experiments will be prioritized by the Principle Investigator according to the cell number available. The results of the laboratory studies will be correlated with the engraftment of each unit in the patients (see Section 14.0).

Immune Recovery

Immune recovery testing will be performed as per current ABMT guidelines.

10.7 Post UCBT Evaluation

Post-transplant evaluations are summarized in the following table. Scheduled evaluations for day 21 should be performed +/-2 days, for day 28 should be performed +4/-2 days. For day 60, evaluations should be performed +/-7 days. For day 100, evaluations should be performed +/- 10 days. For 6 and 9 months should be done +/-14 days, and 1 year, 18 months, 2 years should be performed +/-30 days of the targeted date.

Immune studies will be done per MSKCC standard of care. Evaluations may be with-held at the treating physicians discretion (eg if the patient has relapsed or is critically ill). Also, additional tests will be performed as clinically indicated.

ACTIVITY	DAY 0 TO CB ENGRAFTMENT	ENGRAFTMENT TO DAY +100	LONG TERM FOLLOW-UP
History & physical		1-2 weekly	Month 6, 9, 12, 24
Chemistry	Per standard of care		Month 6, 9, 12, 24
Counts & differential			Month 6, 9, 12, 24
BM studies: morphology, cellularity, & chimerism	Day 21 if indicated* (Aspirate & core)	Day 100 (Aspirate only unless core clinically indicated)*	Month 6, 12 if needed for clinical management
Chimerism: whole blood (DMP Lab)	Day 14, (21 if no BM aspirate done)	Day 60 & 100	Month 6, 12, 24
GVHD evaluation	-	Once or bi-weekly	Month 6, 12, 24
Immune recovery**(per MSKCC standard)	Day 28	Day 60	Month 3-4, 6, 9, 12, 18, 24
Disease evaluation as appropriate	-	Day 100	Month 6, 12
Research Labs			
NK cell recovery	Day 28	Day 60 & 100	Month 6, 12
Serum markers***	1-2 times weekly-day 0 till day 60	Once weekly day 60 to 100	

* If day 21 BM is not possible or the patient can be adequately assessed from the peripheral blood, peripheral blood chimerism should be performed as a substitute. Also, if BM studies are done prior to day 100 for clinical purposes and it is thought that a repeat is not clinically indicated then day 100 studies can be done on blood only.

** Immune function and NK cell recovery testing can be withheld if the patient has very low circulating white blood cells making testing impossible. Also, if immune recovery studies are done for clinical care purposes and it is thought that a repeat is not clinically indicated they can be withheld.

*** These can be withheld if the patient is critically ill.

During the first 100 days patients will be closely monitored as per standard of care. Acute GVHD will be assessed and graded according to MSKCC guidelines. To determine acute GVHD grading, clinical data will be collected weekly or bi-weekly for the first 100 days.

Research blood (1-4 tablespoons/ week) will be obtained to assess the recovery of NK cells and to assess serum biomarkers of immune complications as indicated in the Table.

Note immune studies will not be drawn if the patient has severe cytopenia precluding testing.

10.8 Evaluation > 100 days post UCBT

These should include: history and physical examinations, blood counts and chemistry including liver function tests (CMP) at a minimum of approximately every 6 weeks until 6 months, then at a minimum of approximately every three months for one year, and at approximately 3-6 month intervals until 2 years post transplant. The patient's referring physician, in consultation with the MSKCC transplant physician, may assist with follow-up.

Chronic GVHD will be diagnosed and graded according to MSKCC criteria. Assessments will be obtained at approximately day 100, 6, and 12 and 24 months after transplant and at additional time points as clinically indicated. Patients who develop chronic GVHD will be treated according to the current standard of care.

Bone marrow aspirate with analysis for chimerism and disease status will be performed at 6 months, one year post transplant and other time-points as clinically indicated, with cores as needed.

Immune recovery will be evaluated as per MSKCC BMT standard of care guidelines. Patients will be vaccinated after transplant as per current MSKCC guidelines or as clinically appropriate. Note immune studies will not be drawn if the patient has severe cytopenia precluding testing and IgG levels will not measured per protocol during the time the patient is IVIg dependent.

Also, research blood (approximately 20 cc) will be obtained to assess the recovery of NK and T cells at 6 months and 1 year.

11.1 TOXICITIES/ SIDE-EFFECTS

11.2 Toxicity Grading

Toxicities will be graded according to Adult BMT Guidelines.

11.3 Total Body Irradiation (TBI)

The dose of TBI in this regimen is low and therefore the side-effects that may be associated with high doses of radiation should be minimal. At the dose of radiation in this study mild nausea and vomiting, diarrhea, mucositis, fever, alopecia, and transient erythema may occur but should be mild and can be treated symptomatically.

Radiation contributes to the immune suppression induced by the chemotherapy and immune suppressing drugs. This is a major toxicity of the preparative regimen and is treated by donor stem cell infusion and aggressive supportive care.

High doses of radiation in combination with high dose chemotherapy may contribute to damage to vital organs such as the lung or the liver. Such toxicity is unlikely with the doses in this protocol.

Late effects include cataracts, second malignancies and hypothyroidism and are possible but unlikely due to the low radiation dose. Hypothyroidism will be routinely monitored post transplant and treated with hormonal replacement as indicated. Radiation could contribute to the risk for sterility that is primarily from chemotherapy. The risk increases with the number of years since puberty.

11.4 Cyclophosphamide

Nausea, vomiting and anorexia: virtually all patients will experience nausea and vomiting after intravenous cyclophosphamide. This can be significantly diminished with anti-emetics.

Fatigue.

Diarrhea: most patients develop some diarrhea in the first 1-2 weeks post cyclophosphamide. This is treated symptomatically.

Myelosuppression and immune suppression is a major toxicity and is treated by donor stem cell infusion and supportive care.

Mucositis: most patients will develop mild to moderate mucositis of the oral and GI tracts, which will be managed with supportive care.

Skin changes: transient skin rashes have been described. Alopecia is always seen but is usually reversible.

Hemorrhagic cystitis is a potential complication and can be variable in severity. Severe cystitis is unlikely. The risk of cystitis will be reduced by aggressive supportive care. Fluid weight gain and edema is associated with this fluid flush but is transient and can be treated with diuretics if necessary.

Syndrome of inappropriate anti-diuretic hormone (SIADH) can be seen but is transient and will spontaneously resolve after drug administration.

Cardiomyopathy has been described with cyclophosphamide but is very rare.

High doses of cyclophosphamide may contribute to damage to vital organs such as the lung or the liver. This is unlikely due to the reduced intensity of this protocol.

Late effects include sterility.

11.5 Fludarabine

Jaundice and elevations of liver enzymes have been described.

Transient skin rashes have been described.

Immune suppression is a major toxicity and is treated by donor stem cell infusion and supportive care.

Effects on the nervous system are rare, but if they occur could include confusion, coma, weakness or numbness, loss of balance, difficulty walking, or loss of vision and could be very serious or lethal.

11.6 Thiotepa

Side effects of thiotepa include: alopecia, nausea, vomiting, and diarrhea. Thiotepa can also cause myelosuppression, pancytopenia, sterility and fevers.

Other less likely side effects include dizziness and transient hepatic transaminase elevation. Rare but serious side effects include CNS toxicity manifested by headache, mild cognitive dysfunction, disorientation, confusion, irritability, and bizarre behavior; as well as, interstitial pneumonitis and renal failure.

11.7 Mycophenolate mofetil (MMF)

The major toxicity of MMF is immune suppression which leads to increased risk for infection. This is managed with aggressive supportive care with both prophylaxis and treatment of infectious complications.

Other potential side-effects include myelosuppression, headache, insomnia, aches and pains, rash, nausea, anorexia and diarrhea.

There is also a very rare side effect known as Progressive Multifocal Leukoencephalopathy (PML), which is a progressive disease of the nervous system that can cause severe disability or death. A very small number of cases of PML have been reported in patients treated with MMF. PML can cause hemiparesis, confusion, cognitive deficiencies and ataxia.

11.8 Cyclosporine-A (CSA)

The major toxicity of CSA is immune suppression which leads to increased risk for infection. This is managed with aggressive supportive care with both prophylaxis and treatment of infectious complications.

Renal dysfunction is common and is treated by good hydration and reduction of the dose if necessary. Electrolyte abnormalities involving potassium and magnesium are also common and electrolytes must be closely monitored.

Increased blood pressure is common and is treated with anti-hypertensive medication(s).

Neurological side effects include tremor (common), seizures (rare), confusion, ataxia, cortical blindness (rare), and peripheral neuropathies and are usually reversible with cessation of the medication.

While mild to moderate microangiopathic hemolysis is relatively common, serious thrombotic thrombocytopenic purpura (TTP) is rare.

Gastrointestinal side-effects include anorexia and nausea, swollen gums, and hyperbilirubinemia.

Skin changes include hirsutism and gingival hyperplasia.

11.9 G-CSF (Neupogen)

Side-effects of G-CSF are generally mild, include bone pain, headaches, body aches, fatigue, edema and nausea and are managed with supportive care. Pleuro- or pericarditis are seen rarely and are managed by cessation of the medication and corticosteroids if necessary.

11.10 Blood product and UCB unit infusions

Infusions of blood products may produce volume overload which can be managed with diuretics. They may also induce allergic reactions of variable severity, many of which can be prevented or mitigated by premedications as per standard of care. These products may also transmit serious infections (e.g., CMV, hepatitis, HIV). To circumvent this, blood donors are screened according to AABB and FACT guidelines. All blood products (other than the UCB graft) are irradiated to circumvent the risk of GVHD caused by contaminating lymphocytes.

Toxicities potentially associated with the infusion of the UCB graft include DMSO toxicity and side effects from red cells and may include changes in heart rate or rhythm, changes in blood pressure, fever, chills, sweats, nausea/vomiting, diarrhea, abdominal cramping, headache, dyspnea, presence of DMSO taste and odor, hemoglobinuria, and acute renal failure. However due to the dilution step and pre-medication these toxicities are unlikely. The process of CB engraftment can also be associated with a pre-engraftment syndrome characterized by fever and manifestations of capillary leak syndrome. This process is highly responsive to corticosteroid therapy and this will be treated according to accepted clinical practice.

12.1 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

The primary end-point of this study is the disease-free survival (survival without malignant relapse) at one year post-transplant. Disease free survival at two years and overall disease free survival at one and two years will be monitored as secondary endpoints. Other important outcomes include:

12.2 Failure of Neutrophil Recovery and/or Donor Engraftment

The following definitions will be used:

- The day of neutrophil recovery is the 1st day of 3 consecutive days of absolute neutrophil count (ANC) at or above 500 after the 1st post-UCBT nadir.
- Donor chimerism will be defined as either partial (10-89% donor) or complete ($\geq$ 90% donor) and should be recorded as to whether it is sampled from the patient's marrow or peripheral blood and which UCB unit engrafts (by unit number). If both UCB donors engraft, the total donor chimerism (contribution of each donor added together) as well as the contribution of each donor individually should be documented.
- Primary graft failure = no neutrophil recovery by day 45 (regardless of donor chimerism) *or* autologous recovery (ANC recovery but < 10% donor in blood and BM) by day 45.
- Secondary graft failure = loss of ANC to < 500/μL for 14 consecutive days after initial recovery *or* loss of donor chimerism to < 10% donor after primary donor engraftment has been achieved not due to progressive malignancy within the marrow.
- Successful primary donor engraftment = neutrophil recovery within the first 45 days after transplant and partial/complete donor chimerism ($\geq$ 10%).
- Successful sustained donor engraftment = successful primary donor engraftment without subsequent graft failure beyond 45 days. This will be reported along with the median (range) of total donor chimerism at serial time points post-UCBT.

Patients with suspected graft failure will be evaluated with bone marrow biopsy to assess BM cellularity and assess for residual or recurrent disease, and molecular analyses of marrow. Patients who suffer failure of donor engraftment will be managed with supportive care if they have autologous recovery and adequate hematopoiesis, or re-infused with either a second UCB graft or other stem cell source if they are aplastic. Management of graft failure is as per MSKCC standard of care.

12.3 Graft-Versus-Host Disease (GVHD)

Acute GVHD is manifested by skin rash, nausea, vomiting, diarrhea and ulceration of the intestines, hyperbilirubinemia and hepatitis, and suppressed or delayed recovery of the hematopoietic and immune system. Standard clinical criteria, and histological grading of skin, liver or gastrointestinal pathology where possible, will be used to establish and grade acute GVHD. In the first 100 days after transplant patients will be assessed by a transplant physician for the development of acute GVHD approximately weekly. Data will be collected as per standard practice of the Adult BMT service. Patients with moderate to severe acute GVHD (grade II-IV) will be treated as per standard of care. Patients failing to respond to steroids will be considered for treatment with standard or experimental immunosuppressive agents Chronic GVHD is characterized to varying degrees by sclerosis of lacrimal and salivary ducts, scleroderma-like changes of the skin, chronic inflammation and scarring of the gastrointestinal tract with consequent malabsorption and diarrhea, inflammation of the liver, suppression of the immune system and occasionally other auto-immune phenomena (eg auto-immune hemolysis) or involvement of other organs (eg pulmonary involvement). Chronic GVHD will be diagnosed and graded according to the MSK criteria and treated with standard or experimental immunosuppressive therapy. Patients will be assessed for GVHD at day 100, 6 months, 1, and 2 years.

12.4 Transplant related mortality (TRM)

TRM is defined as death at any time from the commencement of pre-transplant conditioning due to any cause other than disease relapse with the exception of automobile or other accidents. The incidence of TRM at day 180 after UCBT is a secondary end-point of the study. Also, stopping rules are in place to consider cessation of the study if TRM at day 100 after UCBT is in excess of 30%.

12.5 Disease Relapse or Progression

Relapse of malignancy is a secondary endpoint of this study and will be defined by accepted clinical practice eg an increasing number of blasts/malignant cells of recipient origin in the marrow over 5%, by the presence of circulating peripheral blasts, or by the presence of malignant cells in any extramedullary site. Cytogenetic (eg if a diagnosis of CML) or flow cytometric analysis or molecular studies of the marrow and/or peripheral blood may also be obtained for the diagnosis of relapse. Isolated molecular persistence or reappearance of bcr-abl without cytogenetic positivity will not be considered relapse.

12.6 Immunologic Recovery

Immunophenotyping of T, B, and NK cells, and T-cell proliferations in response to non-specific mitogens will be performed at serial time points after transplant to measure immune recovery as outlined in section 10.6. Patients may be re-immunized post-transplant according to the MSKCC guidelines. Immune recovery data will be analyzed at completion of study and interim analysis of immune recovery will be permitted.

13.1 CRITERIA FOR REMOVAL FROM STUDY

If at any time the patient is found to be ineligible for the protocol as designated in the section on Criteria for Subject Eligibility, the patient will be removed from the study. Patients may also be removed from the study if they request to be removed and understand the potential risks of such action. Management will depend on where they are in their treatment course. Such patients will receive appropriate supportive care.

14.1 BIOSTATISTICS

14.2 Clinical Endpoints

This is a phase 2 study of RIC UCBT utilizing double unit grafts in selected patients with acute leukemia, MDS, and Non-Hodgkins lymphoma (see Section 6.1 for disease eligibility criteria). As of July 1 2015, the accrual of 55 patients to the protocol is near complete. Therefore, the protocol is amended to accrue an additional 25 patients for a total of 80 patients. These additional patients will provide a more precise estimate of the disease-free and overall survival in this patient population. With 80 patients transplanted, the one-year overall and disease-free survival probability can be estimated to within ± 0.11.

As of July 2015, 45 patients are evaluable for the one-year disease-free survival endpoint, and 24 of these patients remain alive and disease-free for over one year. An additional 6 patients are under observation but have not failed or been followed for one year to date. To account for the observed results in the expanded study, conditional probability arguments will be used to determine the critical region, the type 1 error and power calculations. If at the conclusion of the 80-patient study, 35 or more patients remain alive and disease free for at least one year, this CBT approach will be considered effective. This study design has type 1 error equal to 0.08 when the one-year DFS rate in the population is 0.20 and the power of the study is 0.89 when the one-year DFS rate in the population is 0.40. These calculations are conditional on observing the first 24/45 patients remain alive and disease free for one year.

The protocol includes a stopping rule for day 100 treatment-related mortality. For the initial cohort of patients, 51 patients were evaluable as of July 2015 and 13 have had treatment-related death. The stopping boundary was not crossed. The stopping rules below will be used to monitor the additional 25 patients for day 100 treatment related mortality.

Failure endpoint	# of failures needed to stop the study	Failure rate in the population	Probability boundary is crossed
Day 100 treatment related mortality	3 in the first 8 patients 4 in the first 14 patients 5 in the first 21 patients 6 within 25 patients	0.10	0.09
		0.35	0.95

At the conclusion of the study, the population recovery rates for hematologic and immunologic factors will be estimated using kernel derived growth curves. Kernel smoothing provides a non-parametric estimate of the population recovery rates over time. These longitudinal measures will be correlated with the characteristics of the engrafting unit, the time to infectious complications, and survival time using a marginal regression model and the time-dependent covariate Cox model. In addition, the time to neutrophil and platelet engraftment, and the time to acute and chronic GVHD will be assessed using the cumulative incidence function.

14.3 Laboratory Studies

Laboratory research studies will be performed investigating:

- The determinants of unit predominance to facilitate the understanding of the biology of double unit UCBT. The results of these studies will be correlated with the engraftment of each unit in the patients testing if the laboratory results predict or correlate with unit predominance in the patient. The Wilcoxon

rank sum test will be used to test the continuous correlates and the Fisher's exact test will be used for the binary correlates.

- Immune recovery and serum markers at serial time points after transplant.

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain written informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

16.1 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA and Principal Investigator include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution, and coordination of the activities of the protocol study team. The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized patient record.

16.2 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.3 Data and Safety Monitoring

The Data and Safety Monitoring Plans (DSM) at Memorial Sloan-Kettering cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: Http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at

MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: http://mskweb2.mskcc.org/irb/index.htm.
There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed, and the monitoring procedures will be established at the time of protocol activation.

17.1 PROTECTION OF HUMAN SUBJECTS

The patient will be responsible for the costs of standard medical care, including the UCB graft, all hospitalizations and any transplant complications. The research tests outlined in Section 18.2 will be done at no cost to the patient.

17.2 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board.

17.3 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

For all other trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to sae@mskcc.org.
The report should contain the following information:
Fields populated from CRDB:

- Subject's initials
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

The PI's signature and the date it was signed are required on the completed report.

Potentially serious toxicities are an expected part of transplant therapy. The reportable serious adverse events (SAEs) will be based on the most recent version of the Adult and Pediatric BMT Adverse Event Reporting Standard Operating Procedures.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

Patients recruited to this study are individuals who are referred for stem cell transplantation as a potentially curative treatment for their malignancy. Prior to consideration for transplant, all patients undergo a series of 1-3 hour consultations discussing the risks and potential benefits of an allogeneic stem cell transplant and the different procedures which are a normal part of the transplant course. The risks and potential benefits of the transplant procedure, as well as the participation in a research protocol are also discussed. All patients entered into our studies provide written informed consent and a copy of this will be included in the patient's medical chart and given to the patient. All research protocols and consent forms are reviewed and approved by the IRB. Informed Consent will be obtained before any protocol-specific procedures are performed. Study investigators and designated staff will fully explain the details of the study as well as details of patient privacy concerning research specific information.

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20.0 APPENDICES

Appendix A: KARNOFSKY SCALE (≥16 years)

The score is defined by the phrase which best describes the activity status of the recipient.

Able to carry on normal activity; no special care is needed.

100 Normal; no complaints; no evidence of disease.
90 Able to carry on normal activity.
80 Normal activity with effort.

Unable to work; able to live at home, care for most personal needs; a varying amount of assistance is needed.

70 Cares for self; unable to carry on normal activity or to do active work.
60 Requires occasional assistance but is able to care for most needs.
50 Requires considerable assistance and frequent medical care.

Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.

40 Disabled; requires special care and assistance.
30 Severely disabled; hospitalization indicated, although death not imminent.
20 Very sick; hospitalization necessary.
10 Moribund; fatal process progressing rapidly.

Appendix B: **The International Prognostic Scoring System (IPSS) for MDS**

	Score Value				
Prognostic Variable	0	0.5	1	1.5	2.0
Marrow blasts (%)	<5	5-10		11-20	21-30
Karyotype[a]	Good	Inter	Poor		
Cytopenia	0/1	2/3			
Risk groups	*Score*				
Low	0				
Intermediate 1 (Int-1)	0.5-1.0				
Intermediate 2 (Int-2)	1.5-2.0				
High	2.5-3.5				

[a] Poor: complex (>2), chromosome 7 abnormalities; good: normal, -Y, 5q-, 20q-; intermediate: other abnormalities.

Appendix C: HCT-CI to assess Comorbidity Score

Co-Morbidity	Definition/compartments	Score if YES	Yes/ No
Arrhythmia	Atrial fibrillation*; atrial flutter*; sick sinus syndrome*, ventricular arrhythmia*	(1)	
Cardiovascular	Coronary artery disease*; congestive heart failure*, myocardial infarction*; ejection fraction ≤ 50 §	(1)	
Inflammatory bowel disease	Crohn's disease*; Ulcerative Colitis*	(1)	
Diabetes	Treated with insulin or oral hypoglycemic drugs*	(1)	
Cerebro-vascular	Transient ischemic attacks*; Cerebro-vascular ischemic or hemorrhagic stroke*	(1)	
Depression/anxiety	Requiring psychological consultation and/or specific treatments	(1)	
Hepatic *(mild)*	Chronic hepatitis § ; Bilirubin >ULN – 1.5 X ULN §; AST/ALT >ULN – 2.5 x ULN §	(1)	
Hepatic *(moderate/severe)*	Liver cirrhosis § ; Bilirubin > 1.5 x ULN §; AST/ALT > 2.5 X ULN §	(3)	
Obesity	BMI > 35 (adults)§; BMI for age ≥ 95% percentile (children)§	(1)	
Infection	Requiring anti-microbial treatment before, during, and after the start of conditioning§	(1)	
Rheumatologic	Requiring Treatment*	(2)	
Peptic ulcer	Confirmed by endoscopy and requiring treatment*	(2)	
Renal	Serum creatinine > 2mg/dl (or >177 µmol/L)§; on dialysis§; prior renal transplantation*	(2)	
Pulmonary *(Moderate)*	DLCO corrected for hemoglobin 66-80% of predicted§; FEV1 66-80% of predicted§; Dyspnea on slight activity§	(2)	
Pulmonary *(Severe)*	DLCO corrected for hemoglobin ≤ 65% of predicted§; FEV1 ≤ 65% of predicted§; Dyspnea at rest or requiring oxygen therapy§	(3)	
Heart valve disease	Except asymptomatic mitral valve prolapse§	(3)	
Prior Malignancy	Treated with surgery, chemotherapy, and/or radiotherapy, excluding non-melanoma skin cancer*	(3)	

* Diagnosed at *any time* in the patient's past history
§ Detected at the time of pretransplant assessment