MSK PROTOCOL COVER SHEET

IL-6 Receptor Blockade to Ameliorate Acute Graft versus Host Disease and Early Toxicity after Double Unit Cord Blood Transplantation in Adults with Hematologic Malignancies

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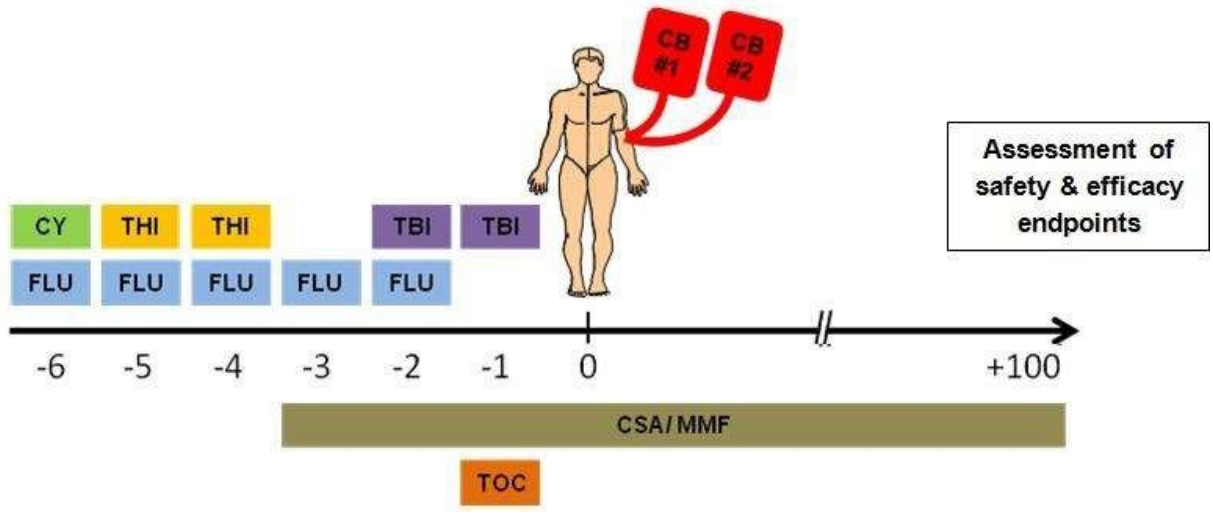
1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is a single-arm phase II study of double-unit cord blood (CB) transplantation (CBT) in adult patients with high risk hematologic malignancies, following intermediate intensity conditioning and standard graft-versus-host disease (GVHD) prophylaxis with cyclosporine (CSA) and mycophenolate mofetil (MMF), with the addition of one dose of tocilizumab (anti-IL6 receptor antibody). The aim of the study is to assess whether the addition of IL6-R blockade to standard GVHD prophylaxis after double-unit CBT will be effective in abrogating the incidence and severity of acute GVHD (aGVHD), pre-engraftment syndrome (PES) and early toxicity after double-unit CBT without compromising patient safety.

Candidates for this trial will include patients aged 18-65 years with acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL), advanced myelodysplasia (MOS), chronic myelogenous leukemia (CML) and other myeloproliferative disorders (MPD) excluding myelofibrosis, or Non-Hodgkin/ Hodgkin lymphoma (NHL/ HL) at high risk of relapse/progression, who are medically fit for allogeneic transplantation and do not have human leukocyte antigen (HLA) matched related or unrelated donors within the indicated time frame. Two partially HLA-matched CB units of adequate size will be used as the graft source.

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 CB graft. This regimen is the current standard of care at MSKCC for adult CBT. Graft-versus-host disease (GVHD) prophylaxis will consist of standard CSA and MMF, with the addition of one dose of tocilizumab (study intervention). This approach is based on published data using adult donor allografts.

Study Schema:



Conditioning: Cyclophosphamide (CY) 50 mg/kg x1 (day -6), Fludarabine (FLU) 30 mg/m^2 x5 (days -6 to -2), Thiotepa (THI) 5 mg/kg x2 (days -5 &-4), Total Body Irradiation (TBI) 200 cGy x2 (days-2 &-1).
GVHD prophylaxis: CSA 3 mg/kg IV q12 hours & MMF 15 mg/kg IV q8 hours starting day -3.
Study intervention: Tocilizumab (TOC) single dose 8 mg/kg IV (capped at 800 mg) on day-1.

Patients will be carefully monitored post-transplant for donor engraftment and count recovery, donor chimerism, the incidence and severity of aGVHD and chronic GVHD (cGVHD), pre-engraftment syndrome (PES), transplant-related mortality (TRM), relapse, speed of immune recovery, as well as overall survival (OS) and disease-free survival (DFS). Additional patient samples will be banked for future use. The analysis of these samples will not be a part of this protocol.

Biostatistics will be based on a total of 45 patients undergoing double-unit CBT per the study schema (the target sample size has been updated since the initiation of the study). The primary endpoint is grade II-IV aGVHD at day 100 post-CBT. It is anticipated that accrual will last approximately 3 years.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary Endpoint:

- Incidence of grade II-IV aGVHD by day 100 after dCBT with Cy/Flu/Thio/TBI400 conditioning, standard GVHD prophylaxis with CSA and MMF, and the addition of one dose of Tocilizumab.

Secondary Endpoints:

- Incidence of grade III-IV aGVHD at 100 days.
- Incidence of grades II-IV and III-IV aGVHD at 180 days and organ distribution.
- Incidence and severity of cGVHD at 1 and 2 years.
- Time to immunosuppression cessation.
- Incidence and time to myeloid engraftment (neutrophil recovery to $\geq$ 0.5 x 10^9/L) and platelet engraftment (unsupported platelet recovery to $\geq$ 20,000 x 10^9/L).
- Contribution of each CB unit to donor chimerism in the first 100 days after CBT.
- Incidence of PES.
- Incidence of TRM at 100 days, 6 months, 1 and 2 years.
- Incidence of relapse at 1 and 2 years after CBT.
- The probability of PFS at 1 and 2 years after CBT.
- The probability of OS at 1 and 2 years after CBT.
- T-cell and B-cell immune recovery in the first two years after CBT.

3.0 BACKGROUND AND RATIONALE

Introduction

Umbilical cord blood (CB) is a valuable alternative hematopoietic stem cell (HSC) source for patients in need of allogeneic transplantation without suitable human leukocyte antigen (HLA)-matched adult volunteer unrelated donors (URDs). Advantages of CB transplantation (CBT) include rapid graft availability [1], significant extension of allograft access to racial/ ethnic minority patients (especially patients of southern European, mixed and non-European ancestry) [2], low rates of cGVHD [3] and a potent graft-versus-malignancy effect [4, 5]. The use of double-unit CBT (dCBT) has extended the application of CBT to older children and adult patients without adequately sized single CB units [6]. Moreover, dCBT has been associated with enhanced protection against relapse in patients with hematologic malignancies [7-10]. Finally, in experienced centers including MSKCC, progression-free survival PFS after dCBT is comparable

to that of 8/8 HLA-matched URD HSC transplants (HSCT) and superior to mismatched URD HSCTs [5, 10, 11] **(Figure 1**). For the above reasons, MSKCC has embraced dCBT as the graft source of choice for patients who are candidates for HSCT without readily available HLA-matched URDs.

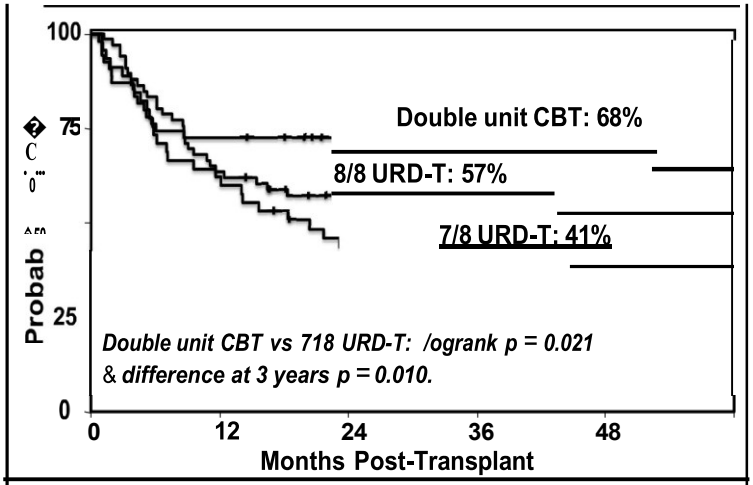


Figure 1. MSKCC 3-year DFS in adult patients with acut leukemia or CML undergoing 7-8/8 URD or dCB ransplants (n=166).

CBT, however, is associated with two major limitations that can hinder transplant success and that may contribute to post-transplant complications. The first limitation is the delayed hematopoietic recovery compared to adult donor grafts [12, 13]. However, due to advancements in CB unit quality and banking, modern algorithms for unit selection, the use of double unit grafts for adults and modern highly-immunosuppressive conditioning regimens, the risk of graft failure has markedly decreased and the speed of neutrophil engraftment has improved in recent years [14, 15]. Moreover, several strategies to further enhance hematopoietic recovery after CBT, including co-administration of a haploidentical or third party stem cell graft with CB graft(s), CB unit ex vivo expansion or priming to improve homing, are under active investigation by our and other institutions.

The second limitation of T-cell replete CBT, which is the focus of investigation in this protocol, is relatively high rates of aGVHD [3, 16] that contribute to early post-transplant morbidity, infectious complications, hospitalization burden and TRM. Multiple recent reports have demonstrated inferior immune reconstitution and worse outcomes in anti-thymocyte globulin (ATG)-based CBT [17-19). Consequently, ATG is no longer recommended as prophylaxis in adult CBT for hematologic malignancies. MSKCC and other institutions have investigated intensifying CSA [20] and MMF dosing [21, 22], or alternative GVHD prophylaxis regimens [23] with some success however severe aGVHD remains a limitation that negatively impacts CBT outcomes. Therefore, the development of novel strategies to ameliorate severe aGVHD and GVHD-related post-transplant complications remains an unmet medical need. Based on promising pre-clinical data and phase 1/11 results in adult donor allograft recipients [24-26], this protocol will investigate whether the addition of IL-6R blockade by a single dose of tocilizumab to standard GVHD prophylaxis may abrogate the incidence of severe aGVHD and early toxicity after dCBT in adults with high-risk hematologic malignancies.

Clinical Results of dCBT in Adults with High Risk Hematologic Malignancies at MSKCC

Since 2008, MSKCC has implemented a novel intermediate intensity conditioning regimen of cyclophosphamide 50 mg/kg, fludarabine 150 mg/m^2, thiotepa 5-10 mg/kg and 400 cGy total body irradiation (TBI). This has been associated with lower toxicity compared to traditional high dose chemo-radiation while maximizing disease control. In an early analysis of the first 30 patients, it was shown that this conditioning regimen provided reliable donor-derived hematopoietic engraftment and was associated with low relapse risk and acceptable TRM [27].

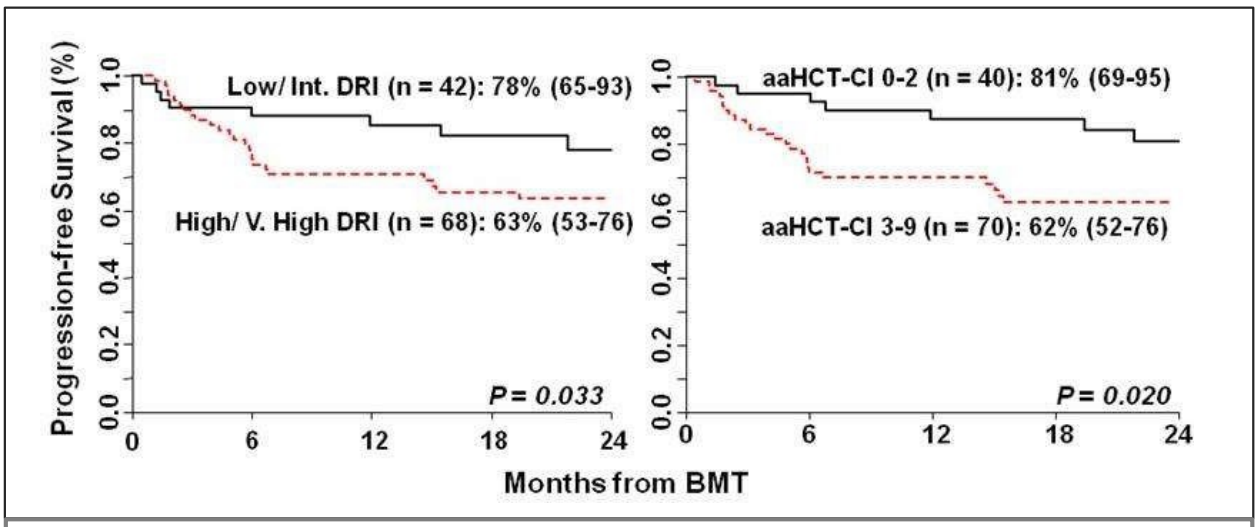


Figure 2. 2-year PFS by rDRI and aaHCT-CI (n=110).

More recently, we have analyzed 110 adult patients with a median (range) age of 51 (18-65) years who underwent first CBT with the above conditioning regimen for the treatment of high risk hematologic malignancies. 109 patients received double unit and 1 single unit CB grafts [median donor recipient 8-allele HLA-match 5/8 (range 2-8); median infused CD34+ dose 0.95 x 10^5/kg/unit (range 0.17-3.72)]. Additionally, 49/110 patients received CD34+ selected stem cells from a haplo-identical donor in addition to the CB graft. GVHD prophylaxis was with CSA/ MMF. 55% of patients were of non-European ancestry. The most common indication for transplant was acute leukemia (n=83), followed by B-cell NHL (n=14), MOS/ MPD (n=11) and HL (n=2). Overall, 96% of patients achieved sustained CB-derived neutrophil engraftment. Day 180 incidences of grades II-IV and III-IV aGVHD were 75% (95%CI: 66-83) and 21% (95%CI: 14-29), respectively. However, the incidence of day 100 grade II-IV aGVHD in recipients of dCBT only (without the addition of haplo-identical CD34+ stem cells), which was used in the sample size calculation for this protocol, was approximately 65%. The cumulative incidence of cGVHD for the entire cohort at 1 year was 8% (95%CI: 4-15). Day 180 TRM incidence was 15% (95%CI: 8-22) and aGVHD was the most common contributor to TRM, followed by organ failure. The 2-year relapse incidence was low 10% (95%CI: 5-17). With a median follow-up of 2.7 years (range 6 months-8.5 years), the 2-year OS was 72% (95%CI: 64-81) and 2-year PFS was 69% (95%CI: 61-79). In univariate analysis, revised disease risk index (rDRI) (low/ intermediate vs. high/ very high) & age adjusted hematopoietic cell transplant-comorbidity index (aaHCT-CI) (aaHCT-CI <3 vs. aaHCT-CI 2:3) were significant determinants of PFS **(Figure 2).** In contrast, recipient age, ancestry, CMV serostatus and graft characteristics were not. In multivariate analysis, only aaHCT-CI remained significant at the 0.05 level [HR 2.15 (95%CI: 1.01-4.59) if aaHCT-CI ≥ 3 (p = 0.047); HR 2.03 (95%CI: 0.92-4.48) if high/ very high rDRI (p = 0.079)].

Based on the above findings, dCBT after intermediate intensity conditioning is associated with high PFS in patients with low comorbidity and affords promising PFS (63% at 2 years) even in patients with high/ very high rDRI, mostly by reducing the relapse rates. However, the incidence of aGVHD is relatively high and aGVHD is a common cause of treatment failure, especially in patients with high aaHCT-CI. Moreover, analysis of hospitalization burden in this patient cohort identified a negative impact of aGVHD on the rates of early readmission and inpatient hospital

stay in the first 6 months after CBT. Specifically, 101/110 (92%) patients survived to first discharge after a median of 37 days (range 14-77) post-CBT (counting BMT index hospitalization from day 0). Within the first 180 days, 60/101 (59%) of these patients were re-admitted for transplant-related complications at least once [111 readmissions, median 1 readmission per patient (range 1-9)), whereas high proportions of patients were outpatient & progression-free beyond 6 months post-CBT **(Figure 3).** Notably, the most common cause of readmission in the first 6 months was aGVHD or infection in the setting of active aGVHD. aaHCT-CI was again identified as the only independent predictor of hospitalization burden. In conclusion, aGVHD greatly contributes to early post-CBT morbidity and management of aGHVD leads to increased resource utilization. Strategies to ameliorate aGVHD after dCBT are greatly needed.

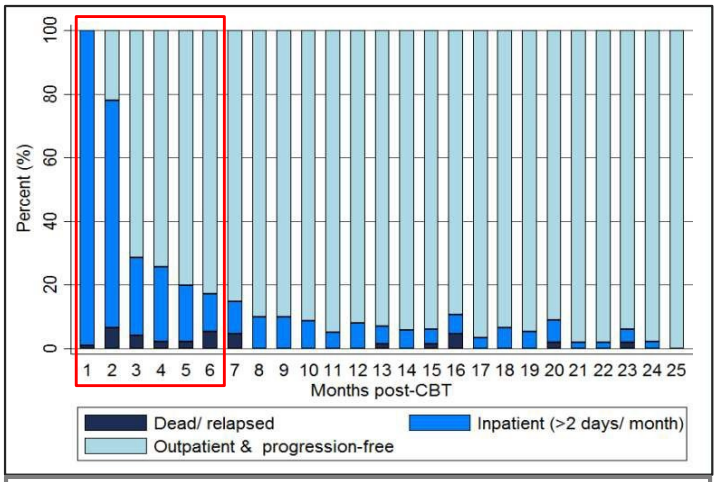


Figure 3. Distribution of pt status (outpatient & progression free vs inpatient vs dead/ relapsed) by post-transplant month (0-2 years).

Rationale for the Investigation of IL-6R Blockade in GVHD Prophylaxis

IL-6 is a pro-inflammatory cytokine that has been implicated in the pathogenesis of aGVHD in murine models [28, 29]. Moreover, high serum IL-6 levels have been correlated with fever, sepsis, mucositis, engraftment syndrome, aGVHD and other inflammatory processes in HSCT recipients [30-37]. In a phase 1/11 study, a single dose of the anti-IL-6R antibody Tocilizumab (8 mg/kg), a humanized antibody that can bind both soluble and membrane bound IL-6R and inhibit IL-6R signaling, given on day-1 in 48 patients undergoing T-cell replete HLA-matched adult donor HSCT in addition to standard GVHD prophylaxis (methotrexate and calcineurin inhibitor) greatly ameliorated the incidence of grades II-IV (12%) and III-IV aGVHD (4%) compared to controls [24]. The intervention was well tolerated and resulted in greatly reduced TRM from GVHD, whereas there was no discernible effect on the relapse risk compared to historical controls. This data has recently been replicated in the U.S. in a smaller phase II trial of 35 patients [25]. Based on the above, this protocol will investigate the application of IL6-R inhibition in addition to standard GVHD prophylaxis in the setting of dCBT, with the hypothesis that this strategy will effectively abrogate the incidence and severity of aGVHD without compromising patient safety.

Moreover, tocilizumab has been successfully used to treat cytokine release syndrome in recipients of CAR-T cells or haploidentical HSCT [38, 39]. Therefore, the application of IL-6R inhibition in the setting of dCBT has the potential additional benefit of reducing the incidence and severity of pre-engraftment syndrome (PES), a frequent complication seen in up to 75% of CBT recipients [40, 41]. PES has been attributed to graft-versus-graft and graft-versus-recipient in the presence of multiple HLA-mismatches by some investigators. It is characterized by cytokine mediated capillary leak and may further complicate early post-CBT care. Specifically, corticosteroid use for the treatment of PES may promote CMV infection and thus may increase morbidity and mortality in CMV seropositive CBT recipients [42]. Based on the above, the impact of IL6-R blockade on the incidence of PES will be studied as a secondary endpoint.

In further support of the investigation of IL-6R blockade in the setting of dCBT, we have measured serial IL-6 levels in 37 dCBT recipients who had serum samples collected weekly in the first month post-transplant and survived for at least 1 month. The median age (range) of the cohort was 52 (24 - 64) years. The median 8-allele HLA match between the engrafting CB unit and the recipient was 5/8 (3/8-7/8). Seven patients developed no aGVHD by day 100, and 30 patients developed grade 1-111 aGVHD by day 100 at a median (range) time of 49 (10-93) days. Four of the 37 (11%) patients developed grade I, 21/37 (57%) developed grade II, and 6/37 (16%) developed grade III aGVHD by day 100. Moreover, 15/37 (41%) patients developed corticosteroid-requiring pre-engraftment syndrome at a median (range) of 13 (10-17). Despite considerable inter-patient variability, serum IL-6 followed similar kinetics overall **(Figure 4).** For the majority of patients, IL-6 levels were below the level of detection of 2.5 pg/ml on day 0, peaked between days 5-13, and subsequently decreased to baseline levels by 28 days post-transplant. Patients who developed corticosteroid requiring PES had overall higher serum IL-6 levels in the first month after dCBT compared to patients who did not **(Figure 5)**. Moreover, comparison of peak IL-6 levels in the first month post dCBT between patients with and without PES showed a strong trend towards higher values in the PES group (p=0.0589) **(Figure 5).** While there was no correlation between IL-6 levels and aGVHD severity, the overall increased IL-6 levels during a time period that PES is observed and allo-interactions generating subsequent aGVHD occur support the pursuit of IL-6R blockade as a novel strategy to further improve CBT outcomes.

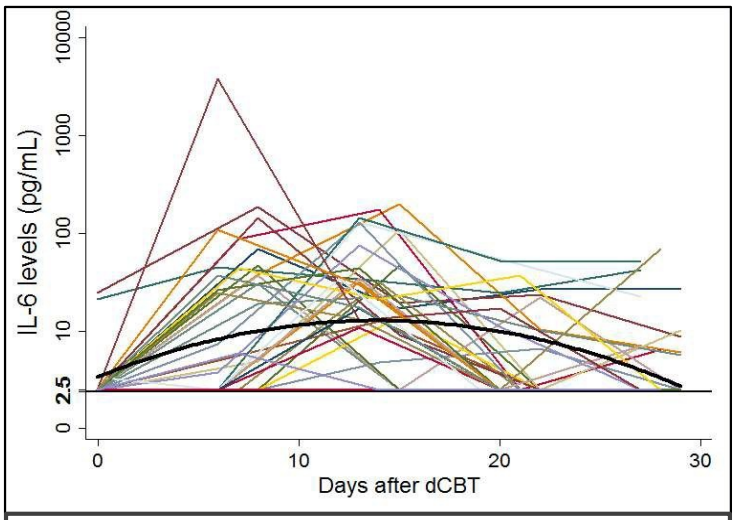


Figure 4. IL-6 levels in first month after dCBT (n=37). Black line represents line of best fit (quadratic).

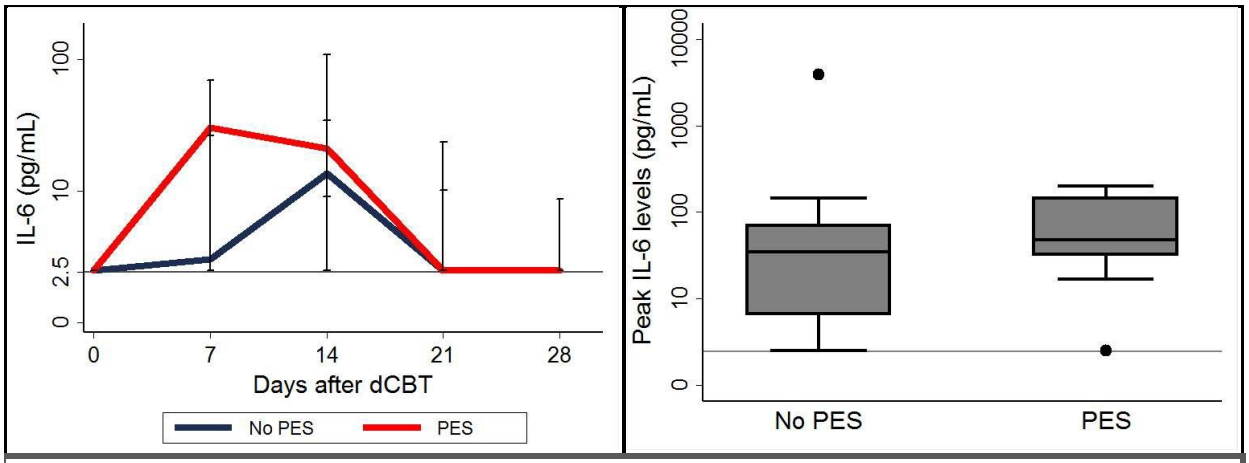


Figure 5. A) Median IL-6 levels in the first month after dCBT in patients with or without PES (whiskers denote interquartile range). **B)** Comparison between peak levels in the first month after dCBT between patient with and without PES (p=0.0589).

Summary

CBT is a potentially curative therapy for patients with otherwise lethal hematologic malignancies. This has great significance for ethnic or racial minority patients who have greatly limited access to matched unrelated volunteer adult donors. In experienced centers, dCBT for adults with high risk hematologic malignancies is associated with comparable survival to transplants from matched URDs and superior outcomes compared to mismatched URD transplants. However, one of the most common causes of treatment failure after ATG-free dCBT that greatly contributes to TRM, morbidity and cost is the relatively high incidence of aGVHD. Based on preclinical studies, the results of two phase 1/11 studies in adult donor allograft recipients and our preliminary data, the addition of IL6-R blockade to standard GVHD prophylaxis is a promising strategy to investigate for the reduction of the incidence and burden of severe aGVHD after dCBT. Moreover this intervention may have a beneficial impact on other post-dCBT complications or toxicities such as PES, corticosteroid use and hospitalization burden. Therefore, it may lead to decreased resource use and transplat cost. If this study is succesful, it has the potential to establish anti-lL-6 antibodies as a cost effective, simple and therefore easily applicable strategy to improve the safety of CBT and therefore may extend allograft access to more patients, especially of non-western European descent who have a low likelihood of finding HLA-matched adult volunteer donors.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a single-arm phase 2 study to investigate whether the addition of one dose of Tocilizumab to standard GVHD prophylaxis with cyclosporine and mycophenolate mofetil will decrease the incidence of severe GVHD and early toxicity in adult patients undergoing double-unit CBT after intermediate intensity conditioning. A Simon's two-stage minimax design was originallyimplemented with a maximum accrual of 27 evaluable patients with high risk hematologic malignancies (16 in the first stage and 11 in the second stage), based on the sample size calculations that are detailed in section 14. Stopping rules are in place to protect subjects from excessive toxicity (TRM or graft failure). The Simon two-stage design was closed after the interim analysis due to lack of efficacy for the primary endpoint. However, due to improvement in key secondary endpoints, the protocol was previously amended to extend the sample size to the originally intended 27 patients. The target accrual for the protocol was further increased to 45 transplanted patients during the study period as detailed in section 14.

4.2 Intervention

Adult patients between 18 and 65 years old with high risk hematologic malignancies and a suitable double-unit CB graft will undergo work-up to assess protocol eligibility. Eligible patients will be consented in the week prior to transplant admission. CB graft selection will be based on established MSKCC guidelines. Patients will receive standard intermediate intensity conditioning with cyclophosphamide 50 mg/kg, fludarabine 150 mg/m^2, thiotepa 10 mg/kg, and total body irradiation 400 cGy. GVHD prophylaxis will consist of cyclosporine-A (CSA) and mycophenolate mofetil (MMF) starting day -3. In addition, patients enrolled in this study will receive one dose of tocilizumab IV (8 mg/kg, maximum dose 800 mg), given on day -1. The double-unit CB graft will be infused on day 0 per standard practice. Post-transplant supportive care will be per standard practice. Patients will be followed clinically for two years after CBT for the assessment of the efficacy and safety endpoints, which will be compared to historic controls with identical eligibility

criteria and transplanted with identical conditioning and GVHD prophylaxis, but without tocilizumab.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 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 24 hours (refrigerated: 6 days)

Preparation:
1. Standard IV fluid: d5w.
2. Final concentration range up to: 20mg/ml.
3. IV piggyback volume: for doses< 700mg, infuse in 25cc d5w; for doses 700-1500mg; 25cc d5w or 50ml 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.

5.2 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. Spike infusion bag with secondary set.

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.
- Note: low dose acyclovir is routinely used in transplant patients for the prevention of HSV/VZV reactivation per standard MSKCC Adult BMT practice, but will not be infused concurrently with fludarabine due to drug incompatibility.

5.3 Thiotepa (Thioplex®)

Supplied as: 15 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 are stable for 24 hours under refrigeration and room temperature.
3. Reconstituted solutions further diluted with NS at concentration of 1 mg/ml, 3 mg/ml and 5 mg/ml are stable for up to 24 hours at room temperature and 48 hours under refrigeration.
4. Diluted solutions of 0.5 mg/ml in NS should be used immediately after preparation.

Clinical considerations:

- Hydration: NA
- Emetic potential: low.
- Supportive medications: none.
- Toxicities: see Section 11.0.
- Incompatibilities: cisplatin, filgrastim (G-CSF), vinorelbine
- Thiotepa may prolong the actions of succinylcholine; use this is combination with caution.
- Instruct patient to shower 1 hour and 6 hours after receiving high-dose Thiotepa to decrease the incidence of folliculitis.
- Instruct patient in mouth care after meals and at bedtime.

5.4 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.

5.5 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 24 hours under refrigeration or at room temperature.

Preparation:

1. Dilute in D5W or NS to make a 2.5 mg/ ml solution. Prepare injections in non DEHP/PVC bags to avoid possible leaching of diethylhexylphthalate (DEHP) from polyvinyl chloride (PVC) containers into injection of cyclosporine.
2. Diluted solutions are stable for 24 hours in D5W and NS for injection.
3. Solutions should be inspected for particulate matter and discoloration prior to administration whenever solution and container permit.
4. 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.
- 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. 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.
    - Note: Acyclovir is routinely used in transplant patients for the prevention of HSVNZV reactivation. Low dose is used to minimize the risk of nephrotoxicity. Acyclovir will not be co-infused with cyclosporine due to drug incompatibility. Because both acyclovir and cyclosporine may be nephrotoxic, the patients' renal function is closely monitored post transplant.

5.6 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.

5.7 Tocilizumab (Acemtra®)

General Information: Tocilizumab is an interleukin-6 (IL-6) receptor (IL-6R) antagonist.

Supplied as: 80mg, 200mg and 400mg single-use vials (20mg/ml)

Supplier: Genentech Inc.

Storage and stability:

1. Tocilizumab injection should be stored between 2-8°C (36-46°F). Do not freeze.
2. Inspect visually for all particulate matter and discoloration. If visibly opaque particles or other foreign objects are observed, the solution should not be used.
3. Upon dilution, final production may be stored under refrigeration or at room temperature for 24 hours.

Preparation:

1. For patients< 30kg, dilute with 50ml 0.9% sodium chloride. For patients≥ 30kg, dilute to 100ml with 0.9% sodium chloride.
2. Slowly add tocilizumab to the IV bag. To mix the solution, gently invert the bag to avoid foaming.
3. Allow the dilution to reach room temperature prior to infusion.

Administration: Administer infusion over 60 minutes with infusion set. Do not give as IV push or bolus.

Clinical considerations:

- Patients should be tested for latent tuberculosis prior to use.
- Do not administer tocilizumab to a patient with active infection.
- Allow solution to reach room temperature prior to infusion.
- Routine use or premedications is not recommended.

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

General information: Filgrastim is a human granulocyte colony-stimulating factor (G-CSF) produced by recombinant DNA technology. NEUPOGEN® is the Amgen Inc. trademark for Filgrastim, which has been selected as the name for recombinant methionyl human granulocyte colony-stimulating factor (r-metHuG-CSF).

Formulation: NEUPOGEN® is a sterile, clear, colorless, preservative-free liquid for parenteral administration containing Filgrastim at a specific activity of 1.0 ± 0.6 x 108 U/mg (as measured by a cell mitogenesis assay). The product is available in single use vials and prefilled syringes. The single use vials contain either 300 mcg or 480 mcg Filgrastim at a fill volume of 1.0 ml or 1.6 ml, respectively. The single use prefilled syringes contain either 300 mcg or 480 mcg Filgrastim at a fill volume of 0.5 ml or 0.8 ml, respectively

Supplier: Amgen, Inc.

Storage and Stability:

1. Store in a refrigerator (2-8°C). Do not freeze.
2. If inadvertently the filgrastim is exposed to freezing temperatures for up to 24 hours, it may be thawed and refrigerated for use.
3. Avoid shaking.
4. Filgrastim may be allowed to reach room temperature for 24 hours prior to use.
5. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit; if particulates or discoloration are observed, the container should not be used.

Dosing and administration: 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.

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.

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.

Contraindications: Prior hypersensitivity to Escherichia coli - derived proteins or filgrastim.

6.0 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 in patients with high risk hematologic malignancies undergoing induction or re-induction chemotherapy. At least one cycle of lymphodepleting chemotherapy is necessary for protocol eligibility. Pre-allograft work-up will be performed by the Allogeneic BMT Service. Eligible patients will be consented by the Adult BMT service and then admitted to the Adult Bone Marrow Transplant Unit for dCBT.

6.1 Subject Inclusion Criteria

Age and Donor Status:

Patients aged 18-65 years at time of consent with no available and suitably matched related or unrelated donor in the required time period.

Diagnosis:

I. Acute myelogenous leukemia (AML):

- Complete first remission (CR1) at high risk for relapse such as any of the following:
  - Known prior diagnosis of myelodysplasia (MOS) 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 MOS, abnormalities of 5, 7, 8, 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 who elects allograft with curative intent over consolidation chemotherapy.
  - Any patient unable to tolerate consolidation chemotherapy as would have been deemed appropriate by the treating physician.
  - Other high risk features not defined above.
- Complete second remission (CR2).
- Primary refractory or relapsed AML with less than 10% blasts before transplant. Persistent/ relapsed AML with cytogenetic, flow cytometric, or molecular aberrations in ;?: 10% of cells are eligible

II. Acute lymphoblastic leukemia (ALL):

- Complete first remission (CR1) at high risk for relapse such as any of the following:
  - White cell count at presentation > 30,000 for B-cell lineage and > 100,000 for T-cell lineage.
  - Presence of any high-risk cytogenetic abnormalities 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

- Persistence or recurrence of minimal residual disease on 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.
- Other high risk features not defined above.

o Complete second remission (CR2).

o Primary refractory or relapsed ALL with less than 5% blasts before transplant. Persistent/relapsed ALL with cytogenetic, flow cytometric or molecular aberrations in ≥5% of cells are eligible.

III. Other acute leukemias: leukemias of ambiguous lineage or of other types e.g. blastic plasmacytoid dendritic cell neoplasm with less than 5% blasts. Persistent/relapsed disease with cytogenetic, flow cytometric or molecular aberrations in ≥5% of cells are eligible.

IV. Myelodysplastic Syndrome (MOS)/ Myeloproliferative Disorders (MPD) other than myelofibrosis:

- International prognostic scoring system (IPSS) risk score of INT-2 or high risk at the time of diagnosis.
- Any IPSS risk category if life-threatening cytopenia(s) exists.
- Any IPSS risk category with karyotype or genomic changes that indicate high risk for progression to acute myelogenous leukemia.
- MOS/ myeloproliferative disorder overlap syndromes without myelofibrosis.
- MOS/ MPD patients must have less than 10% bone marrow myeloblasts and ANC.:::. 0.2 (growth factor supported if necessary) at transplant work-up.

V. Non-Hodgkin lymphoma (NHL) or Hodgkin lymphoma (HL) at high-risk of relapse or progression if not in remission:

- Eligible patients with aggressive histologies (such as, but not limited to, diffuse large B-cell NHL, mantle cell NHL, and T-cell histologies) in CR.
- Eligible patients with indolent B cell NHL (such as, but not limited to, follicular, small cell or marginal zone NHL) will have 2nd or subsequent progression with stable disease/ CR/ PR with no single lesion equal to or more than 5 cm.
- Eligible patients with HL will be without progression of disease (POD) after salvage chemotherapy with no single lesion equal to or more than 5 cm.

Organ Function and Performance Status Criteria:

- Karnofsky score .:::. 70% (inpatient Leukemia service transfers without discharge are acceptable provided patient has equivalent KPS as if were outpatient).
- *Calculated* creatinine clearance .:::. 60 ml/min.
- Bilirubin < 1.5 mg/dL (unless benign congenital hyperbilirubinemia).
- ALT≤ 3 x upper limit of normal.
- Pulmonary function (spirometry and corrected DLCO).:::. 50% predicted.
- Left ventricular ejection fraction greater than 50%.
- Albumin.:::. 3.0.
- Age-adjusted Hematopoietic Cell Transplantation-Comorbidity Index (aaHCT-CI) less than or equal to 7.

Graft Criteria

2 CB units will be selected according to current MSKCC unit selection algorithm. High resolution 8 allele HLA typing and recipient HLA antibody profile will be performed. Unit selection will occur based on HLA-match, total nucleated cell (TNC) and CD34+ cell dose adjusted per patient body weight. The bank of origin will also be taken into account. Donor specific HLA antibodies, if present, will also be taken into consideration and may influence the selection of the graft.

- Each CB unit must be at least 3/8 HLA-matched to the patient considering high-resolution 8-allele HLA typing.
- Each CB unit will be required to have a cryopreserved TNC dose of at least 1.5 x 10^7TNC/ recipient body weight (TNC/ kg).
- Each CB unit will be required to have a cryopreserved CD34+ cell dose of at least 1.0 x 10^5 CD34+ cells/ recipient body weight (CD34+/kg).
- A minimum of one domestic will be reserved as a backup unit.

6.2 Subject Exclusion Criteria

- Indolent NHL or Hodgkin lymphoma with POD after most recent salvage chemotherapy.
- Diagnosis of myelofibrosis or other malignancy with moderate-severe bone marrow fibrosis.
- Any diagnosis without prior immunosuppressive chemotherapy within 3 months of intended admission for transplant.
- Prior checkpoint inhibitors/ blockade in the last 12 months.
- 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, long-term 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. It is anticipated that accrual will last approximately 3 years.

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 who are at greater risk of not having a suitable unrelated adult volunteer donor within the limits of being able to identify a suitable CB graft. Pregnant women are excluded from participation in this study.

8.0 PRETREATMENT EVALUATION

8.1 Standard clinical pretreatment evaluations.

The following tests are done as part of Adult BMT standard of care:

a. Within 30 days prior to admission:
- Complete history, review of systems, physical exam (including performance status).
- CBC with differential, comprehensive metabolic panel including albumin, LOH, PT/ PTT.
- Pregnancy test for females of childbearing age (serum or urine HCG) to be performed within 2 weeks (15 days) of planned treatment. This test is not required in exempt patients, defined as having had: i) bilateral oophorectomy, bilateral salpingectomy or bilateral salpingectomy-oophorectomy, ii) hysterectomy, iii) menopause (no menses 2: 1 year prior to treatment or after completion of all treatment), or iv) surgical sterilization (i.e., tubal ligation or blockage).

b. Within 45 days prior to admission:
- Bone marrow aspirate for morphology, and special studies (surface markers, cytogenetics, FISH and molecular studies) as warranted for documentation of disease status and bone marrow morphology.
- Trephine core must be done if any clinical suspicion of fibrosis including all patients with MOS/ MPD or if clinically indicated.

c. Prior to admission:
- 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).
- EKG.
- Echocardiogram with measurement of left ventricular ejection fraction.
- Radiographic studies as clinically indicated for diagnosis.
- Chest CT scan without contrast to exclude occult fungal infection prior to transplant (unless CT with contrast required for disease assessment eg NHL or clinically indicated evaluation).
- Pulmonary function testing including DLCO corrected for Hb.
- Testing for CMV (lgG and lgM), HIV-1/2, HTLV-1/2, toxoplasmosis, Hepatitis B, Hepatitis C, Herpes Zoster, Epstein Barr Virus, and syphilis.
- Testing for latent tuberculosis by quantiferon, as medically necessary, for patients with risk factors or known exposure to tuberculosis.
- Peripheral blood from the patient should be submitted to the Diagnostic Molecular Pathology (DMP) Laboratory.
- HLA antibodies to the American Red Cross prior to unit selection.
- aaHCT-CI will be assessed and recorded once the organ function studies are resulted.

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.

8.2 Pretreatment Protocol Research Tests.

a. Prior to conditioning:

- Approximately 20 cc (dark green top tubes) should be collected for correlative research studies.

9.0 TREATMENT/INTERVENTION PLAN

Eligible patients will require a triple lumen central venous catheter and will be admitted to the Adult Bone Marrow Transplant Unit for CBT. Patients will be cared for as per standard allogeneic BMT clinical care guidelines.

9.1 Conditioning Prior to dCBT

Day	Treatment
-7	Line placement and admission to Adult BMT
-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 (AM)
-2	Fludarabine 30 mg/m^2 IV TBI 200 cGy
-1	TBI 200 cGy Tocilizumab 8 mg/kg IV
0	dCBT

Cyclophosphamide 50 mg/kg 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).
Tocilizumab 8 mg/kg IV (capped at 800 mg) day -1 (1 dose).

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

- Cyclophosphamide 50 mg/kg should be administered as per MSKCC guidelines on day -6. 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/dose 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.

Appropriate skin care with showering will be done as per MSKCC guidelines on the days of

thiotepa administration.

- Total Body Irradiation (TBI): 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. Patients at risk of CNS and/or testicular relapse can also receive boosts to these areas at the discretion of the BMT and Radiation Oncology Attendings.

9.2 GVHD prophylaxis

All patients will receive standard GVHD prophylaxis with Cyclosporine A (CSA) and Mycophenolate Mofetil (MMF), and in addition they will receive one dose of Tocilizumab on day -1, as follows:

Cyclosporine

- Cyclosporine A (CSA) beginning 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 obesity) starting day -3 and dose adjustments should be made on the basis of toxicity and CSA trough 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, nephrotoxicity), CSA should be discontinued after consultation with the protocol P.I. 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 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 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) 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 current MSKCC MMF guidelines.
- Obtain therapeutic trough levels as per MSKCC guidelines and adjust per guidelines (max dose 1500 mg q8h) on days +1 and +8.
- 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. Do not use liquid suspension.

- No dose adjustments for renal or liver disease are needed routinely unless severe organ dysfunction.
- If patient is ≥ +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 10-20% decrements. The aim to be off the drug by approximately 4-6 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 is 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.

Tocilizumab

- Tocilizumab should be given as a single IV dose of 8 mg/kg (rounded to vial size) on day -1 over approximately 60 minutes (max dose 800 mg).

9.3 CB Thaw and Administration

- Units will be thawed using albumin-dextran dilution 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, ,'.5. 0.5% of the post-thaw TNC of each unit will be used for laboratory research studies.
- 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. CB unit infusion nursing guidelines should be followed.
- Units should be infused as per MSKCC standard of care.

9.4 Growth Factor (G-CSF) after CBT

G-CSF 5 mcg/kg/day SQ (dose rounded to vial size to a maximum of 480 mcg) will be given to all patients post-CBT as from day+7 until ANC recovery. In the case of slow count recovery, consult PI and follow MSKCC guidelines. G-CSF dose can be increased to q12 hours as from day 21 post-CBT if needed per MSKCC guidelines at the discretion of the Attending in the setting of slow engraftment. IV administration can be substituted if SQ is not tolerated.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

10.1 Standard Supportive Care

This will be as per standard MSKCC BMT guidelines.

10.2 Post-CBT Evaluation

Post-CBT evaluations to be performed at the indicated time points (within the appropriate window) per post-CBT period are detailed below.

Time point (post-CBT)	Acceptable window
Day 21	+/- 2 days
Day 28	+/- 2 days
Day42	+/- 4 days
Day 60	+/- 7 days
Day 100	+/- 7 days
4 Months	day 120 +/- 10 days
6 Months	day 180 +/- 14 days
9 Months	day 270 +/- 14 days
12 Months	day 365 +/- 30 days
18 Months	day 545 +/- 30 days
24 Months	day 730 +/- 30 days

Evaluations may be withheld if the treating physician feels that there is a strong contra-indication to perform the study (e.g. patient is critically ill or has relapsed and is terminally ill or patient refusal). Also, additional tests may be performed as clinically indicated.

ACTIVITY	DAY 1 TO ENGRAFTMENT	ENGRAFTMENT TO DAY 100	LONG TERM FOLLOW-UP
Standard of Care Activities			
Karnofsky score	As per standard of care	Day +100	+6, 9, 12, 18, 24 months
History and physical	As per standard of care		+6, 9, 12, 18, 24 months
Chemistry	As per standard of care		+6, 9, 12, 18, 24 months
Counts/ differential			+6, 9, 12, 18, 24 months
BM aspirate with DMP chimerism	Day +21	Day +100	+6, 12 months
Disease specific studies for lymphoid malignancies		Day +100	+12, 24 months
Chimerism: whole blood (DMP Lab)	Day +28	Day +60, 100	+6, 9, 12, 24 months
GVHD evaluation	Per BMT guidelines	Day +100	+6, 9, 12, 24 months
Immune recovery (per MSKCC standard)	Day+28	Day+60	+4,6,9, 12, 18,24 months

Research Labs		
Blood sample collection for correlative laboratory studies	Days 0, +7, 14, 21, 28, 42 and 60	

- 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.
- Day 100 BM aspirate can be forgone for patients in whom bone marrow restaging is not deemed necessary.
- For BM studies, add core/ trephine if clinically indicated.
- Assess remission status appropriate for patient's diagnosis with CT scan and/or PET scan and/or BM studies as appropriate.
- Immune recovery monitoring will be done as per current MSKCC BMT standard practice. Immune function testing can be withheld if the patient has very low circulating white blood cells making testing impossible.

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 for the first 100 days.

Chronic GVHD will be diagnosed and graded according to MSKCC criteria. Assessments will be obtained at approximately 6, 9 and 12 months, and annually 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.

Immune recovery will be evaluated as per MSKCC BMT standard of care. Patients will be vaccinated after transplant once they reach appropriate immune recovery milestones per current MSKCC guidelines or as clinically appropriate and the response to vaccination should be documented. Note immune studies will not be drawn if the patient has severe cytopenia precluding testing.

11.0 TOXICITIES/SIDE EFFECTS

11.1 Toxicity Grading

Toxicities will be graded according to Adult BMT Guidelines.

11.2 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.

11.3 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.

11.4 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.

11.5 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.

11.6 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.

11.7 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.

11.8 Tocilizumab

Tocilizumab is in general well tolerated. It may cause infusion related reactions, headache, dizziness and skin rash. Other potential side-effects include increase in liver function tests, diarrhea, abdominal pain, and increased serum cholesterol.

Rare side effects include allergic reaction, increased risk of infection, low blood pressure, cough, and pneumonia.

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 and pericarditis are seen rarely and are managed by cessation of the medication and corticosteroids if necessary.

11.10 Blood product and CB 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 CB graft) are irradiated to circumvent the risk of GVHD caused by contaminating lymphocytes.

Toxicities potentially associated with the infusion of the CB 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 use of red cell depleted units, the dilution step, hydration and pre-medications 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 standard clinical practice.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

The primary end-point of this study is incidence of grade II-IV aGVHD by day 100 post dCBT. Key secondary safety and efficacy endpoints include: incidence of graft failure, speed and success of neutrophil and platelet engraftment, pattern of donor chimerism, incidence of day 100 grade III-IV aGVHD and day 180 grades II-IV and III-IV aGVHD, incidence of 1-year and 2- year cGVHD, organ distribution of GVHD, incidence of PES, TRM, disease relapse/ progression and immunologic recovery. Definitions for response/ outcome assessment are described below.

12.1 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 first post-CBT nadir.
- Donor chimerism will be defined as either partial (10-89% donor) or complete (.::: 90% donor) and should be recorded as to whether it is sampled from the patient's marrow or peripheral blood and which CB unit engrafts (by unit number). If both CB units 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 complete donor chimerism (.::: 90%).
- 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-dCBT.

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 with 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 CB graft or other stem cell source if they are aplastic. Management of graft failure is as per MSKCC standard of care.

12.2 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 practice of the Adult BMT service. Patients failing to respond to corticosteroids will be considered for treatment with standard or experimental immunosuppressive agents.

Chronic GVHD can affect the eyes, mouth, skin, gut and other organs. It can involve suppression of the immune system and occasionally manifest as other auto-immune phenomena (eg. auto-immune hemolysis). 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 serial time-points up to 2 years post-CBT.

12.3 Pre-engraftment syndrome (PES)

PES is defined as: 1) unexplained fever greater than 38.5° C (101.3° F) not associated with documented infection and unresponsive to antimicrobial manipulations; and/or 2) unexplained

erythematous skin rash resembling that of aGVHD, with either the fever or the rash occurring prior to or at neutrophil recovery. Fevers and rash due to drug reactions should also be excluded.
PES requires prompt recognition and treatment with corticosteroids. However, the administration of tocilizumab on day -1 is expected to result in very low incidence of PES. Consequently, first neutropenic fever > 38.5 C should be managed with escalation of antibiotic coverage as appropriate. For patients with persistent fevers that do not respond to antibiotic manipulation, IV methylprednisolone 1 mg/kg every 24 hours for 3 days should be considered for PES. Response to therapy will be assessed on day 3 after initiation of therapy. CR will be defined as absence of fever beyond 48 hours of treatment initiation and resolution of rash. Patients without CR to initial therapy will be candidates for extended or additional course of corticosteroids.

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 serial time-points after CBT is a secondary end-point of the study. Stopping rules are in place to consider cessation of the study if TRM at day 100 is excessive (see Section 14)

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 Ph+ ALL) 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 (or other molecular markers) 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 per standard of care. Patients may be re-immunized post-transplant according to the MSKCC guidelines.

13.0 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.

14.0 BIOSTATISTICS

This is a single-arm phase 2 study investigating the safety and efficacy of the addition of one dose of tocilizumab (8 mg/kg, capped at 800 mg) to standard GVHD prophylaxis in adult patients with

hematologic malignancies undergoing intermediate intensity dCBT (see Section 6.1 for disease eligibility criteria).

The design of this study was amended in January 2019. The phase II design was closed at the N=16 interim analysis (as described below) due to a lack of efficacy for the primary endpoint of grade II-IV aGVHD by day 100. However, while intervention did not improve grade II-IV aGVHD, there was an initial signal of improvement for key secondary objectives. Therefore, the study was extended to the full N=27 cohort to better estimate the potential effect of tocilizumab on the secondary objectives. The primary endpoint of the study remains grade II-IV aGVHD; the cumulative incidence of grade II-IV aGVHD will be reported along with the 95% confidence interval. The secondary objectives remain the same.

As of May 2019 the protocol is close to achieving accrual. Analysis of outcomes continues to be promising from the standpoint of reduction in severe acute GVHD (grades Ill-IV) as well as the serious early post-transplant complication of pre-engraftment syndrome. No safety concerns have been identified. A larger phase II protocol of this approach with an overall survival primary endpoint is in preparation. In the interim, the accrual to this protocol will be extended to a cohort of 45 transplanted patients. In addition to providing a seamless continuation of patients treated as part a study protocol, these additional patients will add valuable precision for the secondary efficacy and safety endpoints of the study.

Orginal Design:
The primary endpoint of the study is incidence of grade II-IV aGVHD by day 100 post dCBT. Based on historical MSKCC data, the day 100 grade II-IV aGVHD rate is approximately 65% among patients treated with identical conditioning and CSA/MMF GVHD prophylaxis, without the addition of Tocilizumab. This study is going to be considered promising for further investigation if the day 100 grade II-IV aGVHD rate is 40% or less, and considered unpromising if the rate is 65% or more. Using these rates, a Simon's two-stage minimax design will be implemented, with type I and type II errors both set at 0.10. In the first stage of the study, a total of 16 patients will be accrued. If more than 9 patients develop grades II-IV aGVHD by day 100, the study will close due to a lack of efficacy. Otherwise, an additional 11 patients will be accrued. If, at the end of the trial, more than 12 of the 27 patients are free of grade II-IV aGVHD by day 100 post-dCBT, the intervention will be considered promising.

Secondary efficacy and safety endpoints of the study will include incidences of graft failure, incidence of day 100 grade Ill-IV aGVHD and day 180 grades II-IV and Ill-IV aGVHD, incidence of 1-year and 2 year cGVHD, organ distribution of GVHD, time to immunosuppression cessation, speed and success of neutrophil and platelet engraftment, pattern of donor chimerism in the first 100 days, incidence of PES, risk of TRM (100 days, 6 months, 1 and 2 years), and the probabilities of relapse, OS and PFS at 1 and 2 years as listed in the secondary endpoints (Section 2.0, p5).

OS and PFS will be estimated using the Kaplan-Meier method. OS will be defined as the time from transplantation to death from any cause, whereas PFS will be defined as the time from transplantation to progression or death from any cause. The cumulative incidence of neutrophil and platelet engraftment will be calculated within the competing risks framework considering death without neutrophil or platelet recovery, respectively, as completing events. The cumulative incidences of graft failure and PES will be calculated within the competing risks framework considering death without engraftment before day 21 as a competing event. The cumulative

incidence of acute and chronic GVHD, relapse, and TRM will be calculated within the competing risks framework considering relapse/ death without developing GVHD, death in the absence of relapse, and relapse as competing events, respectively. Descriptive statistics will be used to analyze the pattern of unit chimerism, immune reconstitution (T and B-cell recovery in the first 2 years post-CBT), and toxicities according to CTCAEv4.0 as outlined in the Adult BMT guidelines. Outcomes will be compared to double unit CBT historical controls transplanted with identical conditioning and immunosuppression without Tocilizumab.

Samples for future laboratory studies will be banked as part of this protocol; however, the analysis of these samples are not be a part of this protocol.

It is anticipated that accrual will last approximately 3 years. However, in order to reduce patient risk, the study design includes early termination in the event of excessive rates of graft failure or early TRM within the first 100 days post-transplant. The sequential boundaries calculated based on marginal probabilities are provided in the table below.

Stopping Rule Guidelines (N=27 transplanted patients)

Failure endpoint	# of failures needed to stop the study	Projected probability of failure	Probability of boundary crossing
Graft failure	3 in the first 21 patients	0.05	0.09
	4 at any point	0.25	0.95
TRM within 100 days	4 in the first 10 patients 5 in the first 14 patients	0.15	0.10
	6 in the first 18 patients 7 in the first 23 patients 8 at any point	0.40	0.94

Additional Stopping Rules for the expanded sample size.

Stopping Rule Guidelines (Patient 28 to 45; 18 additional transplanted patients)

Failure endpoint	# of failures needed to stop the study	Projected probability of failure	Probability of boundary crossing
Graft failure	2 in the first 7 3 in the first 16	0.05	0.07
	4 at any point	0.30	0.92
TRM within 100 days	3 in the first 6 patients 4 in the first 1O patients	0.15	0.10
	5 in the first 14 patients 6 at any point	0.45	0.92

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain 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. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.2 Randomization

Not applicable.

16.0 DATA MANAGEMENT ISSUES

A Clinical Research Coordinator (CRC) and Clinical Research Associate (CRA) will be assigned to the study. The responsibilities of the CRC, CRA 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.

16.1 Quality Assurance

Bi-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 PI for discussion and action. Random-sample data quality and protocol compliance audits will be conducted by the study team to ensure the quality of the data.

16.2 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: https://one.mskcc.org/sites/pub/clinresearch/Documents/MSKCC_Data_and_Safety_Monitoring_Plans.pdf

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.

17.0 PROTECTION OF HUMAN SUBJECTS

The patient will be responsible for the costs of standard medical care, including the CB graft, all hospitalizations and any transplant complications. The research tests incorporated in this study will be done at no cost to the patient.

17.1 Privacy

MSK'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 (IRB/PB).

The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with other qualified researchers.

17.2 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 participant 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 starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occurs after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
    - An explanation of how the AE was handled
    - A description of the participant's condition
    - Indication if the participant 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

For IND/IDE protocols:

The SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the IND Office.

17.2.1

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.

The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with other qualified researchers.

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
Karyotypea	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: Age-adjusted HCT-CI to assess Comorbidity Score

Co-Morbidity	Definition/compartments	Score if YES	Yes/ No
Age	≥ 40 years	(1)	
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)	
Cerebra-vascular	Transient ischemic attacks*; Cerebra-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