UNIVERSITY OF MINNESOTA BLOOD AND MARROW TRANSPLANTATION PROGRAM

Hematopoietic Stem Cell Transplantation in High Risk Patients with Fanconi Anemia

MT2002-02
CPRC # 2002LS014

Study Committee
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September 4, 2019

Revision History

DATE	PROTOCOL CHANGE
12/17/12	Resolve data collection inconsistencies: •Clarify the secondary objective/endpoint of regimen related toxicity is based on transplant outcomes through day 100 (engraftment, infections, treatment related mortality, etc.) •Patients will be monitored for reportable events through day 100 according to the table in section 8.3, decrease reporting to the DSMC Add arm 4 for registration purposes – Sibling donor, without use of the CliniMACS Add section 4.5 Registration with definition of arms Correct donor inclusion criteria section 4.3.5 Clarify peripheral blood will be used as a cell source only if bone marrow cannot be obtained. Replace Dilantin with Keppra for seizure prophylaxis per current institutional practice Replace Antifungal Therapy section with updated drugs per current institutional practice Update statistical section Update to current IRB and FDA event definitions and reporting requirements Update to current formatting
03/02/2011	Revised eligibility criteria to include only subjects with 1) FA and biallelic BRCA2 mutation, or 2) with FA and aplastic anemia, advanced MDS or acute leukemia who are ineligible for total body irradiation. Added documentation that protocol is conducted under IND 14536 (cover page, sections 9.1.2 and 9.2,
03/24/2010	Section 7.4 Cell Processing – replace Isolex 300i System with CliniMACS® Cell Selection System (Miltenyi Biotec), add protocol to current CliniMACS IDE (D. Weisdorf sponsor); add section 9.1.4 for reporting CliniMAC malfunction to Miltenyi; Section 8.9 Immune Reconstitution – replace reference to terminated protocol MT2001-12 with current protocol MT2009-22R; Section 9 replace with current SAE reporting requirements and DSMP, update risks. Delete appendix I and VII, renumber rest; Additional Minor edits; Update consents
5/12/2008	Updated DSMC plan
8/11/2004	Donor eligibility criteria added
5/5/2004	a) deleted the exclusion criteria 5.2.3 “Malignancy within 1 year of HSCT”, and b) added to the inclusion criteria 5.1.1 2) history of malignancy, currently in remission. Stopping rules in section 9.3 have been amended to include as treatment related mortality (TRM) as a stopping rule Added voriconazole to toxicities
1/26/2004	Peripheral stem cells added as source (sections 3.0, 4.3.1, 7.0, 7.1, 8.6, Appendix VII) Eligibility: recipients must be between 18 and 45 (section 5.1.1) Voriconazole added to fungal therapy (section 6.3.1) Double cord blood added (section 7.2.1, 8.6) Toxicities added for donors (Appendix VII) Todd DeFor, M.S. replaces Anne Goldman Ph.D. as Biostatistician
11/01/2016	Updated protocol to remove IND as all subjects will now be co-enrolled on the HUD protocol. Antifungal therapy updated to current standard of care (section 5.3) Removed standard of care evaluations from the trial (section 7 and Appendix 1) Removed day 21 bone marrow biopsy
09/04/2019	Revised to clarify that post transplant bone marrow aspirates and biopsies will only be performed as clinically indicated Clarified that ATG is dosed every 24 hours Busulfan, ATG, and supportive chemotherapy updated per current pharmacy standard of care Updated reporting requirements to current MCC SOP

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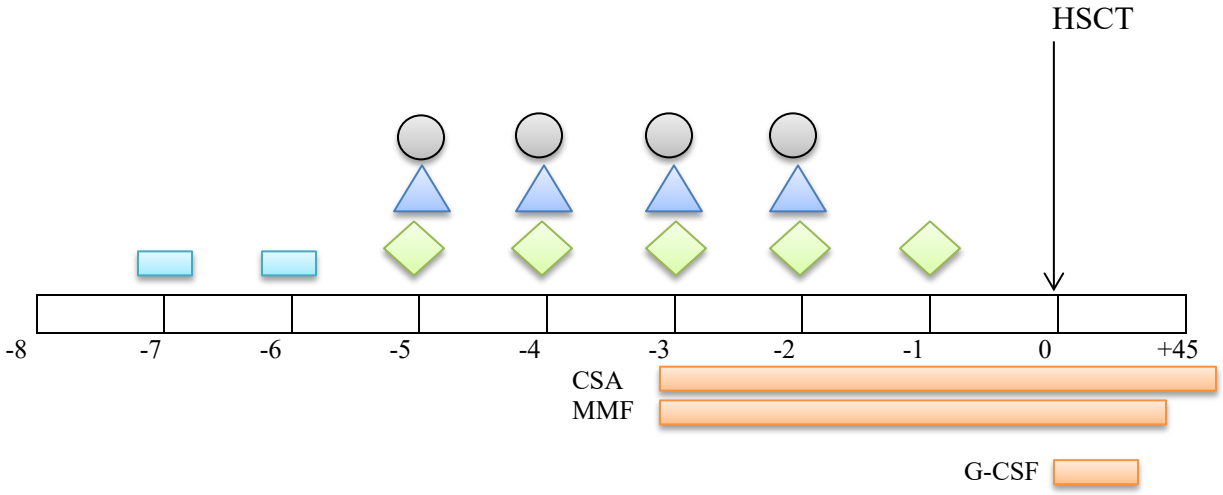
TREATMENT PLAN

possible stem cell sources: related donor BM, unrelated donor BM, UCB

treatment plan:



Busulfan 0.8 mg/kg IV q 12 hours (1.0 mg/kg IV q 12 hours if <4 years old) day -7 and -6

Cyclophosphamide 10 mg/kg IV over 2 hours days -5 through day -2

Fludarabine 35 mg/m^2 IV over 30 minutes days -5 through -2

Antithymocyte globulin or ATG (ATGAM) 30 mg/kg/day IV every 24 hours days -5 through day -1 (Methylprednisolone pre-med 2 mg/kg IV)

1 OBJECTIVES

1.1 Primary Objective

To determine the incidence of neutrophil engraftment in Fanconi Anemia patients with high risk disease treated with busulfan (BU), cyclophosphamide (CY), fludarabine (FLU) and antithymocyte globulin (ATG) followed by HSCT.

1.2 Secondary Objectives

To evaluate:

- incidence of acute and chronic graft-versus-host disease (GVHD)
- incidence of relapse in patients with refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEBt) or acute myeloid leukemia (AML)
- incidence of major infections (gram negative infections, probable or proven fungal infections) in patients with history of major infections
- incidence of regimen-related toxicity (RRT) based on transplant outcomes
- tolerability of mycofenolate mofetil (MMF)
- probability of one year survival

2 STUDY DESIGN

This is a single center study to evaluate the safety, and incidence of neutrophil engraftment in high risk Fanconi anemia patients transplanted with related or unrelated CD34+ selected cells after a cytoreductive preparative regimen consisting of busulfan, cyclophosphamide, fludarabine, and antithymocyte globulin (ATG). Effective with November 1, 2016 protocol, subjects receiving CD34+ selected cells will co enroll on MT2015-31 for T-cell depletion.

3 BACKGROUND

3.1 Overview

HSCT from an allogeneic donor is the only treatment with potential to reverse the hematological complications of FA. Until recently, few patients with a non-HLA identical sibling donors have survived HSCT. However, as a result of a series of phase I studies, we have identified a safe and effective regimen that reproducibly allows for primary engraftment with low risk of regimen related toxicity (RRT) and graft-versus-host disease (GVHD). New data suggest that the success of transplantation is dependent upon the clinical status of the patient at the time of HSCT.[1]

3.2 Results with non-HLA Identical Sibling Donor HSCT: Review of the Literature

For the IBMTR, Gluckman et al. (1995) analyzed the outcome of 199 patients who received HSCT for FA from HLA-identical siblings (n=151), mismatched family member donors (n=29) or unrelated donors (n=19).[2] Age at transplant ranged from 1 to 39 years (median 10 years) for HLA-identical sibling recipients and 4 to 31 years (median 9 years) for non-HLA identical sibling donor recipients. A variety of preparative therapies, GVHD prophylaxis and

supportive care strategies were utilized. For recipients of HLA-identical sibling HSCT, two year probability of myeloid engraftment was 92%. Estimated probabilities of grade II-IV acute GVHD at day 100 was 42% and of chronic GVHD at 2 years 44%. Estimated probability of survival at 2 years was 66%. In multivariate analysis, improved engraftment rates were observed with age of HSCT ≤10 years, conditioning including ATG, and higher platelet count before transplant. In multivariate analysis, decreased mortality was observed with younger age, use of ATG in the conditioning regimen, conditioning with LFI and low-dose CY versus ≥100 mg/kg CY and no irradiation, and the use of cyclosporin with or without methotrexate for GVHD prophylaxis. Patients who received marrow from alternate donors (i.e. donors other than HLA-identical sibling donors) had worse outcomes. Myeloid engraftment was observed in only 76% of patients and grade II-IV acute GVHD occurred in 51%. The probability of survival was 29% after alternative donor transplantation.

More recently, the results of a retrospective multicenter study of 69 unrelated donor HSCTs facilitated through the European Group for Blood and Marrow Transplantation were recently reported by the Paris group.[3] Median age at time of HSCT was 10.8 years (range 4.0 to 37.4 years). Eleven patients (16%) had features of MDS (n = 8) or AML (n = 3) prior to HSCT. Preparative therapy consisted of low dose CY, total body irradiation (TBI) ± ATG in 56% patients, low dose CY, thoracoabdominal irradiation (TAI) ± ATG in 41% patients and chemotherapy ± ATG in 3% patients. The probability of achieving neutrophil recovery by day 30 was 83%. In multivariate analysis, higher probability of achieving neutrophil recovery was associated with younger age (<10 years), a pretransplant elevation of serum alanine/aspartate transaminases (ALT/AST) >2x upper limit of normal, the use of a male donor, and absence of 3-lineage cytopenia before initiation of preparative therapy. Primary graft failure occurred more frequently when female donors were used, mainly due to lower nucleated cell doses compared to grafts from male donors. The probability of severe (grade III-IV) acute GVHD was 34%. Elevated serum ALT/AST before HSCT, limb, urogenital tract or nephrologic malformations, and non-T cell depleted grafts were predictive or severe GVHD. Three year probability of survival was 33%. Among the 14 patients older than 15 years at the time of HSCT, 2 were alive at last follow-up giving a 3 year estimated survival of 14%. In multivariate analysis, extensive congenital malformations, positive cytomegalovirus serology, the use of androgens before HSCT, and female donors were associated with a worse outcome.

In 2012, arm 4 was added in section 4.5 as it was recognized not all sibling donor bone marrow will require cell selection using the CliniMACS. The decision whether or not to do CD34 selection will be made on an individual patient basis.

3.3 Results with non-HLA Identical Sibling Donor HSCT at the University of Minnesota

3.3.1 Results with CY-TBI-ATG

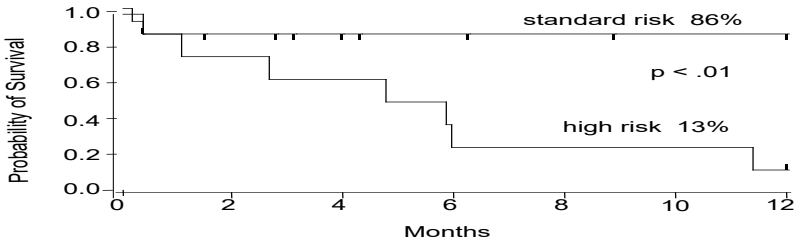
At the University of Minnesota, between June 1993 and July 1998, 29 FA patients were treated with cyclophosphamide 40 mg/kg, total body irradiation (TBI) 450 cGy or 600 cGy and anti-thymocyte globulin (ATG) followed by HSCT from a non-HLA identical sibling donor HSCT.[4] GVHD prophylaxis consisted of cyclosporine A (CSA) for 6 months, short course methylprednisolone (2 mg/kg/d) between day +5 and +19 and TCD by counterflow elutriation in bone marrow recipients. For the entire cohort, the probability of neutrophil recovery was 61% (95%CI 43-79%). In univariate analysis,

factors associated with increased graft failure in bone marrow (BM) recipients were presence of T cell somatic mosaicism (p = .04) and smaller cell dose (<median of 3.4 x 10^7 nucleated cells/kg, p = .05). Of 25 patients evaluable for myeloid engraftment, 3 of 13 patients without T cell somatic mosaicism (< median of 10% DEB insensitive cells) failed to engraft while 7 of 12 patients with T cell somatic mosaicism (>median of 10% DEB insensitive cells) experienced primary graft failure. Probabilities of neutrophil recovery for patients with and without somatic mosaicism were 42% (95% CI 14-70%) and 83% (95% CI 61-100%), respectively (p = .05). Probability of grade III-IV acute GVHD was 28% (95%CI 8-48%). The probability of survival at 1 year was 34% (95% CI 17-51%). Kaplan-Meier estimate of 1 year survival for the entire cohort of 29 patients was 34% (95%CI 17-51%). One year survival in the TBI 450 cGy, TBI 450 cGy with ATG, and 600 cGy with ATG groups, were 43% (95%CI 17-69%), 43% (95%CI 6 - 80%), and 13% (95%CI 0-35%), respectively (p = NS).[4]

3.3.2 Results with FLU-CY-TBI-ATG

Based on all the data from here and elsewhere through 1999, the major obstacle to successful alternate donor HSCT for patients with FA was graft failure. To potentially improve engraftment rate we chose a relatively new immunosuppressive agent, fludarabine (FLU)5-8 to add to the commonly used preparative regimen of cyclophosphamide (CY, 40 mg/kg), total body irradiation (TBI, 450 cGy) and ATG (150 mg/kg). Between April 1999 and November 2001, 27 patients with FA (AA [n=17], RAEB [n=6], RAEBt [n=4]) underwent T cell depleted bone marrow (n=19) or umbilical cord blood transplantation (n=6) from alternate donors (ie. non-HLA-matched sibling donors). Primary neutrophil engraftment was achieved in 25/25 evaluable patients including 9 patients with somatic mosaicism, a potential risk factor for GF. This outcome was of particular significance since the same CY/TBI/ATG regimen but without FLU resulted in only a 63% (95% CI, 42-82%) incidence of engraftment (p<0.01). Notably, secondary GF occurred in 2 recipients of the FLU based regimen at 5 and 7 months after HSCT. OF 25 patients surviving beyond day 21 after HSCT, none developed severe (grade 3-4) acute GVHD. Chronic GVHD has been observed in 2 patients thus far. With a median follow up of 14 months, the probability of survival at 1 year is 46%.

In a recent analysis[1], we stratified the patients on the basis of disease status, a known risk factor that impacts survival in FA patients undergoing HCST.[2, 3] Patients were considered high risk if they had advanced myelodysplastic syndrome (MDS, i.e. refractory anemia with excess blasts [RAEB] or refractory anemia with excess blasts in transformation [RAEBt]), acute myeloid leukemia (AML) or a history of systemic gram negative or



invasive fungal infection. Of note, systemic risk patients (n = 18) had a high probability of survival ((86%, 95% CI 67-100%). In contrast, as shown in the figure below, patients with high risk disease (n = 9) had a significantly lower survival (13%, 95% CI 0-36%, p<0.01).

Therefore, we elected to terminate enrollment of high risk patients onto the FLU-CY-TBI-ATG regimen and develop a novel treatment regimen for high risk patients in an attempt to improve survival without compromising engraftment. Standard risk patients which have done exceptionally well, will continue to receive the FLU-CY-TBI-ATG regimen as detailed in protocol MT 1999-05.

3.3.3 Summary

In summary, the addition of FLU to CY, TBI and ATG is associated with superior engraftment in patients undergoing alternate donor HSCT as compared to all prior regimens without FLU. However, survival remains poor specifically in FA patients with advanced disease.

3.4 Rationale for Proposed Novel Treatment Regimen

Based on the data here as shown above, a new approach is needed for patients with high risk FA. Busulfan is effective chemotherapeutic agent against leukemia and myelodysplasia.[9] Furthermore, it may eliminate the need for TBI which is toxic to FA patients potentially increasing their risk of infection (i.e., by increased breakdown of the mucosal barrier of the gastrointestinal tract). While the use of TBI is standard of care for patients with FA undergoing HSCT, TBI may play a role in the increased risk for the development of late malignancies. If engraftment can be achieved with busulfan without increased toxicity, this therapy may be applicable to standard risk patients in the future in an attempt to decrease the risk of late effects (malignancy, sterility and endocrinopathies).

3.4.1 Busulfan Mechanism of Action

Busulfan (BU) is an alkylating agent with profound myeloablative and anti-leukemic properties. It is frequently used in preparative regimens prior to HSCT as a irradiation sparing agent.[9-11] The levels of oral busulfan have been shown to be quite variable, presumably due to marked differences in absorption and/or clearance.[12] In addition, there is some suggestion that increased plasma levels may relate to enhanced toxicity, while inadequate levels may be associated with graft failure.[13] The recent availability of an intravenous form of the drug may result in decreased variation of the pharmacokinetics of the drug.[14] The drug has been tested in children using a dose of 0.8 mg/kg; however, it was determined that in children less than 4 years of age the clearance was more rapid and in this population a dose of 1.0 mg/kg will be used.[15]

3.4.2 Busulfan Based Preparative Therapy for HSCT for FA Patients

There have been a few case reports published in the literature using BU as preparative therapy in patients with FA as shown in the chart below. The BU dose has varied considerably. Nevertheless, patients have experienced durable engraftment and favorable outcome with tolerable amounts of regimen related toxicity.

Reference	Conditioning Regimen	Number of Cases	Sustained Engraftment	Outcome
Flowers et al., 1992[16]	CY 100 mg/kg + BU 14 mg/kg PO	1	1/1	Died, day 4
Ratanatharathorn et al., 1993[17]*	BU 8 mg/kg PO + TLI 5Gy	2	2/2	Alive >20 mos Died, day 45
Maschan et al, 1997[18]*	BU 8mg/kg PO + CY 40 mg/kg	1	1/1	Alive >17 mos
Ebell et al., 2001[19]	BU 2 mg/kg IV + FLU 180 mg/m2 + ATG	8	8/8	6 Alive
Kato G. (personal communication)	BU 16 mg/kg PO CY 200 mg/kg	1	1/1	Alive 17 years

* Advanced MDS patients

3.5 Schema for HSCT for Patients with FA

In summary, the decision of when to transplant a patient with FA and with which preparative therapy depends on the patient's age, risk status and type of available donor.

4 PATIENT/DONOR SELECTION AND REGISTRATION

4.1 Patient Inclusion Criteria

4.1.1 Patients must be <45 years of age with a diagnosis of Fanconi anemia with Biallelic BRCA2 mutations or
Aplastic anemia, or advanced MDS (MDS with ≥5% blasts), or acute leukemia who are ineligible for total body irradiation. Aplastic anemia is defined as having at least one of the following (with or without cytogenetic abnormalities):

- platelet count <20 x 10^9/L
- ANC <5 x 10^8/L
- Hemoglobin <8 g/dL

Patients must have an HLA-A, B, DRB1 identical or 1 antigen mismatched related or unrelated BM donor or have an HLA-A, B, DRB1 identical, 1 antigen or 2 antigen mismatched related or a suitable unrelated umbilical cord blood (UCB) donor. Patients and donors will be typed for HLA-A and B, DRB1 using high resolution molecular typing. Related donors will be evaluated under the University of Minnesota donor protocol MT2012-14C.

4.1.2 Adequate major organ function including:

- Cardiac: ejection fraction >45%
- Hepatic: no clinical evidence of hepatic failure (e.g. coagulopathy, ascites, no cirrhosis)
- Karnofsky performance status >70% (age 16 years and older) or Lansky Play Score >50 (16 years and younger) – appendix I

4.1.3 Women of child bearing potential must be using adequate birth control and have a negative pregnancy test

4.2 Exclusion Criteria

4.2.1 Active CNS leukemia at time of HSCT

4.2.2. Active uncontrolled infection within one week of HSCT

4.2.3 Pregnant or lactating female

4.3 Donor Inclusion Criteria

4.3.1 In good health based on review of systems and results of physical examination

4.3.2 Normal hemoglobin, white count, platelet count and PTT, and a negative DEB test

4.3.3 HIV-NAT negative, HTLV-1, HTLV-2 negative, Hepatitis B and C negative

4.3.4 Female donors of childbearing potential must have a negative pregnancy test

4.3.5 Must agree to PBSC donation in the event sufficient BM cells are not collected

4.4 Donor Exclusion Criteria

4.4.1 Donor is a lactating female

4.5 Patient/Donor Registration

The eligibility checklist will be completed at the time of study enrollment. Upon completion of the screening evaluation and obtaining consent, the study coordinator or designee will enroll the patient and donor (if related) into OnCore®, the Masonic Cancer Center's clinical database.

The patient will be assigned to one of the following preparative arms based on cell source:
Arm 1: BM using the Isolex 300i System (closed September 2010)
Arm 2: UCB (co-enroll in MT2011-13r for unmanipulated UCB's)
Arm 3: BM using the CliniMACS (effective October 2010) Subjects enrolled on the November 1, 2016 version of the protocol will co-enroll on University of Minnesota Protocol MT2015-31 "CliniMACS CD34 Reagent System as a HUD for Obtaining CD34+ Cell-Enriched Products"
Arm 4: Sibling donor without use of the CliniMACS

The decision whether or not to do CD34 selection will be made on an individual patient basis.

5 PREPARATIVE THERAPY/IMMUNOSUPPRESSIVE THERAPY

In order to provide optimal patient care and to account for individual medical conditions, investigator discretion may be used in the prescribing of all supportive care therapy (i.e. acetaminophen, diphenhydramine, G-CSF, antimicrobials, etc.).

Treatment Plan:

Day	Treatment Plan
-8	Admit to start levetiracetam (Keppra)
-7	Busulfan 0.8 mg/kg IV q 12h (1.0 mg/kg IV q 12h if <4 years old)
-6	Busulfan 0.8 mg/kg IV q 12h (1.0 mg/kg IV q 12h if <4 years old)
-5	Cyclophosphamide 10 mg/kg IV Fludarabine 35 mg/m2 IV Methylprednisolone 2 mg/kg IV q 24h Antithymocyte globulin (ATGAM) 30 mg/kg/day IV q 24 hours
-4	Cyclophosphamide 10 mg/kg IV Fludarabine 35 mg/m2 IV Methylprednisolone 2 mg/kg IV q 24h Antithymocyte globulin (ATGAM) 30 mg/kg/day IV q 24 hours
-3	Cyclophosphamide 10 mg/kg IV Fludarabine 35 mg/m2 IV Methylprednisolone 2 mg/kg IV q 24h Antithymocyte globulin (ATGAM) 30 mg/kg/day IV q 24 hours
-2	Cyclophosphamide 10 mg/kg IV Fludarabine 35 mg/m2 IV Methylprednisolone 2 mg/kg IV q 24h Antithymocyte globulin (ATGAM) 30 mg/kg/day IV q 24 hours
-1	Methylprednisolone 2 mg/kg IV q 24h Antithymocyte globulin (ATGAM) 30 mg/kg/day IV q 24 hours
0	HSCT
+1	Initiate G-CSF 5mcg/kg/day IV (continue until ANC $\geq 2.5 \times 10^9$/L)

5.1 Preparative Therapies

The preparative cytoreductive therapy will be identical for all patients. Treatment related toxicities are defined in the Appendix IV.

All drugs will be prepared and administered per institutional guidelines, with the drugs, doses and scheduled modified as clinically indicated.

Busulfan
As seizures have occurred following high dose busulfan, all patients will be treated with Keppra beginning the night before the first dose of Busulfan (day -8) and continuing until day -4 per institutional guidelines.

Busulfan 0.8 mg/kg IV (with dose of 1.0 mg/kg IV for children <4 years of age) over 2 hours to be given q 12 hours for 2 days for a total dose of 3.2 mg/kg (4.0 mg/kg if <4 years of age).

Busulfan administration and monitoring (including BU levels) should be performed per institutional guidelines. Dosing may be based on Bayesian pharmacokinetics if available or in consultation with inpatient pharmacists using Long-Boy model[23].

Cyclophosphamide
Cyclophosphamide 10 mg/kg is to be given as a 2 hour infusion for 4 days for a total dose of 40 mg/kg. Strict attention should be made to vigorous hydration, fluid balance and maintenance of good urine output. Mesna (10 mg/kg/day) in divided doses will be given on the same days as cyclophosphamide for 4 days for a total dose of 40 mg/kg per institutional guidelines.

Fludarabine
Fludarabine 35 mg/m^2 will be given IV over 30 minutes daily for 4 days for a total dose of 140 mg/m^2.

5.2 Immunosuppressive Therapies

5.2.1 Graft Failure Prophylaxis

Methylprednisolone 2 mg/kg/day intravenously every 24 hours will be given on days -5, -4, -3, -2 and –1, immediately prior to the infusion of antithymocyte globulin (ATGAM).

Antithymocyte globulin (ATGAM) 30 mg/kg every 24 hours will be administered after each dose of methylprednisolone on days -5, -4, -3, -2 and -1. Antithymocyte globulin will be diluted in sterile normal saline or half normal saline for intravenous infusion to a concentration of 1-2 mg/mL and will be infused through the Hickman catheter over 4-6 hours. In the event of a significant reaction to antithymocyte globulin (ATGAM), further doses of the agent will not be administered.

If the patient does not tolerate ATGAM, they will receive the following:

- Thymoglobulin 3 mg/kg IV q24h. Patient will still receive methylpred 2 mg/kg IV q24h as a premed.

5.2.2 GVHD Prophylaxis

Patients will receive cyclosporine A (CSA) and mycophenylate mofetil (MMF) as GVHD prophylaxis.

CSA

Patients will receive CSA therapy beginning on day -3 with a taper commencing on day +100 for matched sibling donor (MSD) recipients and day +180 for non-MSD recipients. For adults with normal baseline renal function (creatinine <1.2 mg/dL), the initial CSA dose will be 2.5 mg/kg IV over 2 hours every 12 hours; for children <45kg, the initial dose will be 2.5 mg/kg IV over 2 hours every 8 hours. CSA dosing will be monitored and altered as clinically appropriate per institutional pharmacy guidelines.

MMF

Patients will receive MMF therapy beginning on day –3 until day +45 inclusively. MMF will be given at a dose of 15 mg/kg/dose (max 1000mg) IV/PO TID adjusted to tablet sizes of 250 mg and 500 mg as per institutional guidelines. MMF may be given IV at the same dose if PO not tolerated.

5.3 Antifungal Therapy

Patients will receive anti-fungal prophylactic therapy with itraconazole, posaconazole, caspofungin or micafungin or per current standard of care beginning up to 1 month prior to conditioning therapy. Antifungal prophylaxis will be given until at least 100 days after HSCT.

6 STEM CELL COLLECTION, PROCESSING AND INFUSION

Preference will be made for the use of bone marrow cells as the stem cell source for patients from either related donors or unrelated donors. Peripheral blood stem cells will only be used if a donor is unwilling or unable to undergo bone marrow cell collection. If a suitable donor is not available in a timely fashion, unrelated donor umbilical cord blood will be used as the stem cell source.

6.1 Bone Marrow

Unrelated donor bone marrow will be collected in the usual sterile manner using established parameters determined by the National Marrow Donor Program.

Related donors will be evaluated and collected per MT2012-14C. Related donor bone marrow will be collected per institutional guidelines.

In August 2016, the University of Minnesota received approval to use the CliniMACS CD34 Reagent System as a Humanitarian Use Device (HUD) as protocol number MT2015-31. With the November 2016 amendment, we will be using MT2015-31 to co-enroll subjects needing CD34+ cell isolation. A minimum of 5.0 x 10^8/kg nucleated bone marrow cells will be collected. CD34+ cells will be isolated from the bone marrow using the CliniMACS® Cell Selection System (Miltenyi Biotec) from unrelated donors and selected related donors.

Related BM may or may not be T-cell depleted as determined on a per patient basis according to current T-cell depletion guidelines.

Infusion will be according to the current University of Minnesota guidelines.

Peripheral blood stem cells will be used only if bone marrow cannot be collected as BM and UCB are the preferred stem cell source. PBSC will be collected and processed per institutional guidelines.

6.2 Umbilical Cord Blood

For those patients without an HLA identical unrelated donor or HLA identical or 1 antigen mismatched related donor, UCB will be the stem cell source of choice. The UCB graft may be composed of 1 or 2 UCB units. The final UCB graft must contain at least 2.5×10^7 nucleated cells/kg recipient weight (or 1.7×10^5 CD34+ cells/kg recipient weight, if known) based on cell numbers at time of cryopreservation. Cord Blood units should be selected according to current University of Minnesota Umbilical Cord Blood Graft Selection Algorithm.

Cord blood products are thawed and filtered (170-micron) in the Molecular and Cellular Therapeutics (MCT) Lab.

Infusion will be according to the current University of Minnesota guidelines.

7 SCHEDULE OF STUDY ACTIVITIES

7.1 Schedule of Activities – refer to appendix I

Scheduled evaluations prior to engraftment (day 30) may be performed +/-3 days from the targeted date; assessments to be performed between engraftment and day 100 may be done +/-7 days of the targeted date; assessments after day 100 may be performed +/-30 days of the targeted date. In addition, targeted days may be altered as clinically appropriate.

7.2 Pre Study Screening Procedures

- Urinalysis and 24 hour urine creatinine clearance or GFR.
- Pregnancy test (urine) - as clinically indicated
- CMV titer (donor/recipient)
- Chest radiograph, high resolution chest CT, sinus CT, and other radiographic studies (as clinically indicated)
- Tumor characteristics at sites of involvement including CT scan of head, chest, abdomen and pelvis (if clinically indicated)
- Bone marrow aspirate and biopsy
- Karnofsky or Lansky performance status (Appendix I)
- Ultrasound of liver and kidneys (within 3 months of HSCT)

- If history of androgens and liver US normal, CT scan of abdomen with contrast to assess for hepatic adenoma. If both ultrasound and CT scan negative, MRI abdomen to assess for adenoma.
- Pulmonary functions tests (children >6 years, adults)
- ECG; echocardiography with left ventricular ejection fraction
- Infectious disease consultation

7.3 Evaluation During Therapy Until Engraftment

- CBC with platelet count daily until one week after ANC $\geq 5 \times 10^8$/L, PLT $\geq 20 \times 10^9$/L
- Review for events per section 8 and for the BMT database
- After BM infusion, GVHD evaluation weekly and as clinically indicated

7.4 Evaluation Post Engraftment To Discharge

- Physical examinations weekly until discharge
- CBC with platelet count weekly until discharge
- GVHD evaluations as clinically indicated
- Test peripheral blood and/or bone marrow for chimerisms as clinically indicated
- Review for toxicity/events per section 8 and for the BMT database

7.5 Evaluation Post Engraftment at Day 60, 100, 180, and 365 and then Once Yearly until 2 Years after HSCT

- CBC, differential and platelet
- GVHD score
- Physical exam
- Bone marrow aspiration, biopsy at day 100, 180 and 365 days if clinically indicated
- Donor chimerism by peripheral blood VNTR at day 60
- Tumor characteristics and sites of involvement
- Patient characteristics evaluated at each visit (Karnofsky or Lansky scale, weight, age)
- Review for events/toxicity per section 8 and for the BMT database
- Clinical Summary at close of study 2 years after BMT or, at death (obtain autopsy report if available)

7.6 Engraftment Evaluation

Peripheral blood CBC counts will be monitored daily after transplantation until engraftment and weekly after engraftment while hospitalized. CBC counts will be evaluated at follow-up visits in the outpatient clinic. Chimerism assay of the bone marrow will be sent on day 21, day 60, day 100, day 180, and day 365 and once a year for 2 years. If the patient's peripheral blood counts are slow to recover, (i.e. ANC $<5 \times 10^8$/L by day 30) or the peripheral blood counts drop below 1×10^9/L after an initial recovery, the peripheral blood and bone marrow will be evaluated. Patients diagnosed with graft failure (ANC $<5 \times 10^8$/L by day 45) must be reported.

7.7 Residual/Recurrent Disease Evaluation

Patients with leukemia will be evaluated routinely for histological evidence of leukemia by bone marrow examination at day 21, 60, day 100, day 180, day 365 and annually thereafter for a maximum of 2 years. If at any time recurrent disease is suspected, additional analyses of

the peripheral blood and bone marrow will be performed. When appropriate, molecular or cytogenetic diagnostic tests will also be performed to detect residual or recurrent disease.

7.8 Immune Reconstitution

Patients should be considered for the University Of Minnesota protocol MT2009-22R - Monitoring of Immune Function and Minimal Residual Disease in Patients and Donors After Hematopoietic Cell Transplantation (HCT).

8 ADVERSE EVENT MONITORING AND REPORTING

Toxicity and adverse events will be classified according to NCI's Common Terminology Criteria for Adverse Events V 4.0 (CTCAE). A copy of the CTCAE can be downloaded from the CTEP home page:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

8.1 Definitions

The following definitions are based on the Code of Federal Regulations Title 21 Part 312.32 (21CFR312.32(a)).

Adverse Event: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction: Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Life-Threatening Adverse Event Or Life-Threatening Suspected Adverse Reaction: An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death.

Serious Adverse Event Or Serious Suspected Adverse Reaction: An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- 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 that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate 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.

Unexpected adverse event or unexpected suspected adverse reaction: An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the protocol-related documents (e.g. protocol, consent documents, investigator brochure, package insert) or is not listed at the specificity or severity that has been observed or given the characteristics of the subject population being studied

Attribution: is the relationship between an adverse event or serious adverse event and the study dru g. Attribution is assigned as follows:

- Definite – The AE is clearly related to the study drug
- Probable – the AE is likely related to the study drug
- Possible – the AE may be related to the study drug
- Unlikely – the AE is doubtfully related to the study drug
- Unrelated – the AE is clearly not related to the study drug

Attribution must be assigned by the treating physician or the PI.

The following definitions are from the Masonic Cancer Center's Standard Operating Procedure (SOP) Deviation Reporting:

Major Deviation: A deviation or violation that impacts the risks and benefits of the research; may impact subject safety, affect the integrity of research data and/or affect a subject's willingness to participate in the research. Deviations that place a subject at risk, but do not result in harm are considered to be major deviations.

Minor Deviation: A deviation or violation that does not impact subject safety, compromise the integrity of research data and/or affect a subject's willingness to participate in the research.

Expedited (Rapid) Reporting: Certain events may require rapid notification to entities providing patient safety oversight (e.g. IRB) as detailed in section 8.2. For the IRB this is 5 working days.

FOR CD34+ SELECTED CELLS ONLY: Any clinically significant safety issues associated with cell processing failure or device malfunction regarding the CliniMACS® system must be reported to the PI (Dr. Margaret MacMillan) and Miltenyi (boston@miltenyibiotec.com) per institutional procedures under protocol MT2015-31.

FOR UNLICENSED UCB UNITS ONLY: These patients will be co-enrolled on University of Minnesota protocol MT2011-13R. **Selected expected adverse reactions** determined to be caused by or probably caused by the UCB unit based on objective evidence will be reported in an expedited manner to the FDA under University of Minnesota IND BB-14797 (C. Brunstein, MD, PhD – sponsor/investigator). Included are the following:

- The unit is mislabeled or failure to pass local lot release
- Serious infusion reaction within first 24 hours after infusion

- Recipient bacteremia with clinical signs and symptoms related to a contaminated UCB within 24 hours after infusion

8.2 Adverse Event Monitoring

Patients will be monitored for excessive treatment related toxicity through day 100 and reported as applicable per section 8.3. After day 100 and upon knowledge, only those events meeting the definition of expedited reporting will be submitted to the appropriate entity per section 8.3

The incidence of graft failure, treatment related morality, opportunistic infection, and GVHD will be monitored as part of the secondary objectives. These events may not necessary constitute a serious adverse advent; however such events may count toward early study stopping rules as detailed in section 10.3.

8.3 Reporting Requirements

Agency reporting to	Criteria for reporting	Timeframe	Form to Use	Submission address/email address
U of MN IRB	Unanticipated death of a locally enrolled subject(s); New or increased risk; Any adverse event that require a change to the protocol or consent form – refer to the IRB website for complete details	5 Business Days	IRB Report Form	irb@umn.edu
	Clinical deviations per current IRB reporting requirements		OnCore Deviation Form	
	1) Serious and unexpected suspected adverse reaction or 2) increased occurrence of serious suspected adverse reactions over that listed in the protocol or investigator brochure or 3) findings from other sources (other studies, animal or in vitro testing)	no later than 15 Calendar-Days		
Masonic Cancer Center SAE Coordinator	Events that meet the definition of dose limiting toxicity or an early study stopping rule (see section 10.3)	At time of reporting	Event Form	mccsaes@umn.edu

The SAE Coordinator will provide the Masonic Cancer Center's Data and Safety Monitoring Council (DSMC) with the SAE in an appropriate format depending on the individual SAE (as reported or in a summary format).

9 DATA AND SAFETY MONITORING PLAN

The study's Data and Safety Monitoring Plan will be in compliance with the University of Minnesota Masonic Cancer Center's Data & Safety Monitoring Plan (DSMP), which can be accessed at http://z.umn.edu/dmsp

For the purposes of data and safety monitoring, this study is classified as moderate risk. Therefore the following requirements will be fulfilled:

- The Masonic Cancer Center Data and Safety Monitoring Council (DSMC) will review the trial's progress twice yearly
- The PI will comply with at least twice yearly monitoring of the project by the Masonic Cancer Center monitoring services.
- The PI will oversee the submission of all reportable adverse events per the definition of reportable in section 8.3 to the Masonic Cancer Center's SAE Coordinator, the University of Minnesota IRB, and the FDA.

In addition, at the time of the continuing review with the University of Minnesota IRB, a copy of the report with any attachments will be submitted to the Cancer Protocol Review Committee (CPRC).

10 STATISTICAL CONSIDERATIONS

It is anticipated that we will enroll a total of 25 patients. Patients will be stratified on the basis of donor type (HLA genotypically identical versus other donor).

10.1 Objectives

The primary objective of this study is to estimate the probability of engraftment. The incidence of GVHD, relapse, major infections, transplant-related mortality (at day 100) and cumulative proportion surviving at 1 year will also be evaluated. The plan is to enroll a maximum of 25 patients in a single arm study.

10.2 Statistical Analysis

There will be continuous monitoring of graft failure. The goal is that graft failure (day 30) be <10% with an upper limit of 25%. Analysis of secondary objectives will consider the incidence of acute GVHD, chronic GVHD, opportunistic infections, relapse (to MDS or AML), and cumulative proportion surviving at 1 year. These will be estimated using cumulative incidence[20] and by the cumulative proportion event-free (by Kaplan-Meier

estimates) and their confidence intervals.[21] Early mortality will be a competing or a censoring event, respectively for the two methods. Confidence levels of 90% will be used because of the small number of available patients.

10.3 Toxicity Monitoring and Early Stopping Rules

Graft failure will be monitored with a type I error rate of 10% to increase the probability of stopping early and because of the small sample size. Stopping boundary for graft failure (H_0 P=0.10 vs. H_1 P=0.25): stop for 2 graft failures in the first 2 patients, 4 of 8 or 5 of 25. This has a type I error rate of 10% if the actual rate is 0.10 and a power of 79% to detect a rate as high as 0.25 at an average sample size of 17.5 patients. If the actual graft failure rate were only 0.20, the power is lowered to 59%. Because graft failure is likely to be more of a problem for those with unrelated donors, the same stopping boundary will be used for that group alone. The smaller sample size and problems with multiple testing are ignored.[22]

The monitoring boundary will be set up based on an overall goal of terminating the study if more than 38% of patients have treatment related mortality by day 100 post transplant.

The monitoring boundary for this study is:
4/4 death, 5/5, 6/7, 7/10, 8/13, 9/25

This boundary has a type I error rate of .10 if the true event rate is approximately 25% and a power of 0.65 for a rate of 38%[22]

10.4 Data Collection

Data collection will include those data that are routinely recorded for related and unrelated donor transplants with special attention to neutrophil engraftment and donor chimerism. Protocol summaries will be available to the protocol chair when requested and as needed for standard Cancer Center safety monitoring procedures.

11 ETHICAL AND REGULATORY CONSIDERATIONS

11.1 Inclusion of Women and Minorities

While there will be every effort to seek out and include women and minority patients, the patient population is dependent upon the referral pattern and the ability to locate a suitable unrelated marrow donor. Women and minority patients are eligible for all aspects of the study and their participation will be actively encouraged. It is recognized that certain minority groups are less likely to find suitably compatible unrelated BM donors through the NMDP registry. Formal efforts to increase minority donor recruitment are being made by the NMDP in order to enhance the availability of this treatment option to all minorities. All minority patients with suitable unrelated BM donors will be actively encouraged to enroll in this pilot study.

11.2 Monitoring

The sponsor-investigator will permit study-related monitoring, audits, and inspections by the IRB, government regulatory bodies, and University of Minnesota compliance groups in addition to the monitoring requirements of the Cancer Center's Data and Safety Monitoring

Plan (section 9). The investigator will make available all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data, etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.) will be available for trial related monitoring, audits, or regulatory inspections.

11.3 Record Retention

The investigator will retain study records including source data, copies of case report forms, consent forms, HIPAA authorizations, and all study correspondence in a secured facility for at least 6 years after the study file is closed with the IRB and FDA.

In addition, the Clinical Trials Office (CTO) will keep a master log of all patients participating in the study with sufficient information to allow retrieval of the medical records for that patient. Please contact the CTO before destroying any study related records.

11.4 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted at sites where IRB approval has been obtained. The protocol, informed consent, written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the investigator.

11.5 Informed Consent

All potential study participants will be given a copy of the IRB-approved consent document to review. The investigator or designee will explain all aspects of the study in lay language and answer all questions regarding the study. If the participant decides to participate in the study, he/she will be asked to sign and date the consent document. Patients who refuse to participate or who withdraw from the study will be treated without prejudice.

12 REFERENCES

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APPENDIX I - SCHEDULE OF ACTIVITIES FOR EACH PATIENT

Activity	Pre-BMT	Day +1 to Engraftment	Post-engraftment to Discharge (days <30 minimum)	Short-term Post-engraftment Follow-up (days 31-100 minimum)	Long-term Post-engraftment Follow-up (>day 100)
Informed consent	x(admission)				
Clinical evaluation	x(admission)	x(1)	x(1)	x(2, discharge home)	x(day 180, 365, 720)
Karnofsky/Lansky score	x(admission)		x(discharge)	x (100, discharge home)	x(day 180,365, 720)
Laboratory evaluation	x(admission)				
CBC/differential	x(admission)	x(1)	x(1)	x(2)	x(day 180, 365, 720)
Cr/Cr clearance	x(admission)	x(1)			x(3)
CXR	x(admission)				
PFT	x(admission)				x(3)
ECG/MUGA/ LVEF	x(admission)				x(3)
US liver & kidneys	x(admission)				
MRI liver	x (3)				
CT head, chest, abd, pelvis	x(3)				
Bone Marrow biopsy, aspirate, Chimerism assay	If clinically indicated	If clinically indicated	If clinically indicated	If clinically indicated	If clinically indicated
GVHD evaluation		x(1)	x(1)	x(3)	x(3)

x(1)=perform test daily x(2)=perform test weekly
x(3)=perform test as clinically indicated x(day)=perform test on day indicated

APPENDIX II- GRAFT VERSUS HOST DISEASE STAGING

Acute GVHD:
Consensus Clinical Stage and Grade of Acute GVHD (Glucksberg *et al*, 1974; Thomas *et al*, 1975, Przepiorka *et al*, 1995)

Stage	Skin	Liver	Lower Gastrointestinal Tract	Upper Gastrointestinal Tract
1	Maculopapular rash <25% of body surface	Bilirubin 2.0 – 3.0 mg/dl	Diarrhea 500 – 1000 mL/day or 280 – 555 mL/m^2	No protracted nausea and vomiting
2	Maculopapular rash 25-50% body surface	Bilirubin 3.1 – 6.0 mg/dl	Diarrhea 1000 – 1500 mL/day or 556 – 833 mL/m^2	Persistent nausea, vomiting or anorexia
3	Generalized erythroderma	Bilirubin 6.1 – 15.0 mg/dl	Diarrhea >1500 mL/day or >833 mL/m^2	
4	Generalized erythroderma with bullous formation and desquamation	Bilirubin > 15 mg/dl	Severe abdominal pain, with or without ileus, or stool with frank blood or melena	

University Of Minnesota Acute GVHD Grading

Acute GVHD Grade	Skin Stage	Liver Stage	Lower GI Stage	Upper GI Stage
I	1-2	0	0	0
II	3	1	1	1
III	-	2-4	2-3	
IV	4	-	4	

- Each column identifies minimum criteria for organ grade.
- Each grade is based on maximum stage for each individual organ involved

e.g. Grade II = skin stage 3 and/or liver stage 1 and/or gut stage 1 and/or UGI stage 1

Chronic GVHD:

Limited CGVHD
Localized skin involvement (<50% body surface area)
and/or
Limited hepatic involvement (abnormal LFTS; bilirubin < 3 mg/dl)

Extensive CGVHD
The presence of one or more of the following criteria may be used for the diagnosis of extensive CGVHD:

- Generalized skin involvement (≥ 50% body surface area)
- Liver histology consistent with involvement by CGVHD with bilirubin ≥ 3 mg/dl
- Positive Schirmer's test (< 5 mm wetting)
- Histologically-proven involvement by CGVHD of oral mucosa or salivary glands
- Lung dysfunction with bronchiolitis obliterans with no evidence of viral causation on histology.
- Gastrointestinal involvement: malabsorption and/or weight loss due to anorexia without explanation other than CGVHD.

APPENDIX III - PERFORMANCE STATUS SCALE

KARNOFSKY PERFORMANCE STATUS SCALE

Percentage	
100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most of his/her needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled, hospitalization indicated. Death not imminent
20	Very sick, hospitalization necessary, active supportive treatment necessary
10	Moribund, fatal processes, progressing rapidly
0	Dead

Reference
Karnofsky DA. Editorial: Meaningful clinical classification of therapeutic responses to anti-cancer drugs. Clin Pharmacol Ther 2:709-712, 1961.

LANSKY PLAY STATUS SCALE

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

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APPENDIX IV - STUDY RELATED TOXICITIES

Toxicities associated with the preparative therapies:

Busulfan

Common	Less Common	Rare
• low white blood cell count with increased risk of infection • low platelet count with increased risk of bleeding • low red blood cell count (anemia) which may cause tiredness, headache, dizziness • hair loss or thinning, including face and body hair (usually grows back after treatment) • long-term or short-term infertility (inability to have children) in men and women	• tiredness • sores in mouth or on lips • fever • nausea • vomiting • rash • loss of appetite • diarrhea • serious infection due to low white blood cell count	• abnormal blood tests results which suggest that the drug is affecting the liver (Your doctor will discuss the importance of this finding, if any.) • allergic reaction with hives, itching, headache, coughing, shortness of breath, or swelling of the face, tongue, or throat • scarring of lung tissue, with cough, difficulty breathing, and shortness of breath that may occur after prolonged use, or even months or years after stopping the drug • leukemia (several years after treatment) • darkened skin • heart problems with high-dose treatment, most often in people with thalassemia (a type of genetic anemia that is present at birth) • problems with the hormone system that cause weakness, tiredness, poor appetite, weight loss, and darker skin • death due lung damage, bone marrow shutdown, sepsis (severe infection) or other causes

Fludarabine

Common	Less Common	Rare
• low white blood cell count with increased risk of infection • low platelet count with increased risk of bleeding • low red blood cell count (anemia) with tiredness and weakness • tiredness (fatigue) • nausea • vomiting • fever and chills • infection	• pneumonia • diarrhea • loss of appetite • weakness • pain	• numbness and tingling in hands and/or feet related to irritation of nerves • changes in vision • agitation • confusion • clumsiness • seizures • coma • cough • trouble breathing • intestinal bleeding • weakness • death due to effects on the brain, infection, bleeding, severe anemia, skin blistering, or other causes

Cyclophosphamide		
Common • low white blood cell count with increased risk of infection • hair loss or thinning, including face and body hair (usually grows back after treatment) • nausea • vomiting • loss of appetite • sores in mouth or on lips • bleeding from bladder, with blood in urine • diarrhea • long-term or short-term infertility (inability to have children) in women and men	**Less Common** • low platelet count with increased risk of bleeding • darkening of nail beds • acne • tiredness • infection • fetal changes if pregnancy occurs during cyclophosphamide	**Rare** • heart problems with high doses, with chest pain, shortness of breath, or swollen feet • severe allergic reactions • skin rash • scarring of bladder • kidney damage (renal tubular necrosis) which can lead to kidney failure • heart damage, with trouble getting your breath, swelling of feet, rapid weight gain • scarring of lung tissue, with cough and shortness of breath • second cancer, which can happen years after taking this drug • death from infection, bleeding, heart failure, allergic reaction, or other causes

Anti-Thymocyte globulin (ATG) -

Common Occurs in 21-100 people out of 100	**Less Frequent** Occurs in 5-20 people out of every 100	**Uncommon** Occurs in <5 people out of every 100
fever chills leukopenia pain headache abdominal pain diarrhea hypertension nausea thrombocytopenia peripheral edema dyspnea asthenia hyperkalemia tachycardia	malaise dizziness	severe allergic reaction (anaphylaxis)

Toxicities associated Immunosuppressive Therapies

Cyclosporine (CSA)	Mycophenolate Mofetil (MMF)
• nephrotoxcity • seizures • hypertension • hirsutism • increased risk of relapse • thrombotic thrombocytopenic purpura • electrolyte imbalances • paresthesias/neuropathy • gingival hyperplasia • increased risk of opportunistic infection	• pancytopenia • headache • insomnia • electrolyte imbalances • leg cramps/bone pain • hypertension • dizziness • hyperglycemia • rash • nausea/diarrhea

Haploidentical Hematopoietic Stem Cell Transplantation

- nausea and vomiting
- possible allergic reaction (including itching, hives, flushing [red face], shortness of breath, wheezing, chest tightness, skin rash, fever, chills, stiff muscles, or trouble breathing)
- graft-versus-host-disease (GVHD)
- veno-occlusive disease,
- mucositis,
- infections (sepsis)

UCB Infusion

Infusion of cord blood may be associated with expected and unexpected adverse events similar to those seen with transfusion of fresh and cryopreserved blood products. Expected adverse events include:

- acute hemolytic reactions
- febrile nonhemolytic reactions
- allergic reactions
- anaphylactoid or anaphylactic reactions
- transfusion-related acute lung injury (TRALI)
- DMSO toxicity
- transmission of bacterial, viral or protozoal infection
- fat embolism (marrow)
- bleeding
- transfusion-associated circulatory overload (TACO)
- hypothermia
- non-immunologic hemolysis
- granulocyte-related complications

Cardiotoxicity associated with double cord blood infusion has also been reported.

G-CSF

bone pain headaches body aches fatigue nausea/vomiting	insomnia dyspnea rash edema