Masonic Cancer Center
University of Minnesota
Blood and Marrow Transplantation

Busulfan and Cyclophosphamide Followed By Allogeneic Hematopoietic Cell Transplantation In Patients With Hematological Malignancies

MT2011-20C
CPRC #2011OC139

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Revision History

Revision #	Version Date	Detail of Changes	Consent change? (Y/N)
	08/06/2012	Original to CPRC and IRB	
1	11/20/2014	section 5.3.1 and 5.3.2- correct the type and number of donor cells to collected section 8 – update event reporting to new IRB requirements	treatment appendix only – replace fludarabine with cyclophosphamide
2	01/30/2017	Treatment plan; Section 5.0 Updated chemotherapy with standard departmental guidelines Section 7.0 – deleted day -1 bone marrow biopsy	Updated with new IRB out of study contact language
3	04/19/2018	Updated GVHD prophylaxis from CSA to tacrolimus per current institutional standard of care	Treatment appendix only – replace CSA with TAC

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Synopsis

Busulfan and Cyclophosphamide Followed By Allogeneic Hematopoietic Cell Transplantation In Patients With Hematological Malignancies

MT2011-20C

This is a treatment guideline to allow routine clinical data to be collected and maintained in OnCore and the University Of Minnesota Blood and Marrow Database as part of the historical database maintained by the department.

Eligible patients will include individuals who have acute leukemia and myelodysplastic syndrome, are ≤ 35 years of age and who have had a previous hematopoietic cell transplant (HCT) or have received sufficient radiation treatment to be ineligible for TBI containing preparative therapy

Study Design: This is a single arm trial to evaluate the efficacy of busulfan and cyclophosphamide followed by an allogeneic hematopoietic stem cell transplant (HSCT) in the treatment of hematological malignancies. The intent of this proposal is to provide a protocol that will use unmanipulated allogeneic hematopoietic stem cells from related and unrelated donors after a common preparative regimen. Results will be compared to historical controls.

Eligibility Criteria: Patients must have a diagnosis of ALL, AML or MDS, currently be in a complete remission and meet one of the following:

- <45 years of age who are at least 6 months after initial HSCT
- <45 years of age and have received sufficient radiation treatment to be ineligible for TBI containing preparative therapy

Karnofsky performance status >70% or Lansky play score >50

Adequate organ function defined as:

- Cardiac: ejection fraction >45%
- Renal: glomerular filtration rate (GFR) >40 mL/min
- Hepatic: no clinical evidence of hepatic failure (e.g. coagulopathy, ascites)

Exclusions – eligible for TBI containing prep; active uncontrolled infection within 1 week; pregnant or breastfeeding

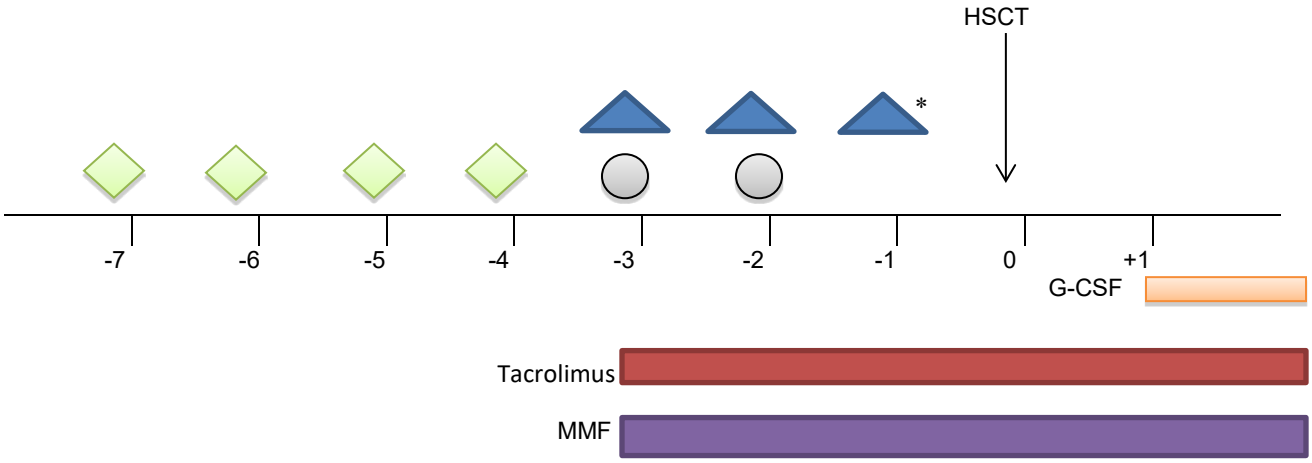
Endpoints Duration of long-term disease-free survival (DFS), rate of engraftment, incidence and severity of acute and chronic graft versus host disease (GVHD), treatment related toxicity and incidence of relapse. Endpoints will be abstracted from routine data collected by the BMT Database.

Enrollment 2-3 patients per year

Treatment Plan

Acceptable stem cell sources include: HLA-matched related or unrelated donor bone marrow (6/6 or 5/6 antigen match), related or unrelated peripheral blood stem cells, and related or single or double unrelated donor umbilical cord blood (6/6, 5/6 or 4/6 match)

Begin levetiracetam (Keppra®) day -8 per institutional busulfan guidelines



Busulfan per institutional guideline for every 6 hours dosingIV) day -7 through day -4

Cyclophosphamide 60 mg/kg/day IV day -3 and -2

G-CSF 5 mcg/kg/day (max 480mcg) IV starting day +1 until ANC ≥2.5 x 10^9/L for 3 consecutive days

* **ATG (Atgam® - equine)** will be administered to **umbilical cord blood recipients only**: 30 mg/kg/dose IV every 24 hours on days -3, -2, and -1.

Standard GVHD prophylaxis or, if eligible, an alternative GVHD prophylaxis will be used:

Tacrolimus will start day -3 for all patients and continue based on stem cell type:

- For patients receiving HLA-identical sibling HCT, beginning on day +100 or 1 month after control of GVHD (whichever is later), Tacrolimus will be tapered by 10%/week.
- For patients receiving alternate donor HCT, beginning on day +180 or 1 month after control of GVHD (whichever is later), Tacrolimus will be tapered by 10%/week.

MMF will start day -3 for all patients and continue to day +30 *or* 7 days after engraftment, whichever is later,

1.0 Introduction

This treatment guideline provides a mechanism that will use unmanipulated allogeneic hematopoietic stem cells from related or unrelated donors after a common preparative regimen in patients with acute leukemia or a myelodysplastic syndrome (MDS) who have either had a prior HSC transplant or have had sufficient radiation therapy preventing the use of total body irradiation (TBI) as part of a transplant preparative regimen.

Major endpoints are duration of long-term disease-free survival (DFS), rate of engraftment, incidence and severity of acute and chronic graft versus host disease (GVHD), treatment related toxicity and incidence of relapse.

Patients will consent to allow routine registration data to be collected and maintained in OnCore, the Masonic Cancer Center's (MCC) clinical database and specific transplant related endpoints in the University of Minnesota Blood and Bone Marrow Database as part of the historical database maintained by the department.

2.0 Background

The treatment guideline is based on the previous University of Minnesota clinical trial "MT2000-12 Busulfan, Cyclophosphamide, and Melphalan Followed by Allogeneic Hematopoietic Cell Transplantation in Patients with Hematological Malignancies;" however melphalan has been omitted to decrease the regimen related toxicity.

3.0 Patient Selection

3.1 Diagnosis of ALL, AML or MDS and currently in complete remission meeting one of the following:

- <45 years of age who are at least 6 months after initial HSCT
- <45 years of age and have received sufficient radiation treatment to be ineligible for TBI containing preparative therapy

3.2 Karnofsky performance status >70% or if < 16 years of age, a Lansky play score >50

3.3 Adequate major organ function including:

- cardiac: left ventricular ejection fraction > 45% by ECHO/MUGA
- renal: creatinine clearance >40 mL/min/1.73m^2
- hepatic: no clinical evidence of hepatic failure (e.g. coagulopathy, ascites)

3.4 An acceptable source of stem cells according to current University of Minnesota BMT program guidelines. Acceptable stem cell sources include:
- HLA-matched related or unrelated donor bone marrow (6/6 or 5/6 antigen match)
- HLA-matched related or unrelated donor peripheral blood stem cells
- related or single or double unrelated donor umbilical cord blood (6/6, 5/6 or 4/6 match)

3.5 Women of child bearing age must have a negative pregnancy test and all sexually active participants must agree to use effective contraception during study treatment

3.6 Written consent (adult or parent/guardian)

3.7 Exclusion Criteria:
- eligible for TBI containing preparative regimen
- active uncontrolled infection within one week of study enrollment
- pregnant or lactating female

4.0 Registration in OnCore

Patients will be registered to this study in OnCore after the signing of the consent.

5.0 Treatment Plan

5.1 Preparative Regimen

The preparative regimen administration and adjustments will follow the University Of Minnesota Blood and Marrow Transplant Program dosing guidelines. Appropriate age/weight dose adjustments will be made for pediatric patients. The treating physician may make chemotherapy drug and dosage adjustments consistent with the standard of care as needed for patient safety.

Day	Therapy
-8	start allopurinol, if appropriate, and levetiracetam (Keppra)
-7	busulfan IV over 2 hours every 6 hours
-6	busulfan IV over 2 hours every 6 hours
-5	busulfan IV over 2 hours every 6 hours
-4	busulfan IV over 2 hours every 6 hours
-3	cyclophosphamide 60 mg/kg/day IV over 2 hours
-2	cyclophosphamide 60 mg/kg/day IV over 2 hours
-1	rest
0	Infusion of stem cells

As seizures have occurred following high dose busulfan, all patients will be treated with levetiracetam (Keppra®) beginning day -8 and continuing until at least 24hours after last busulfan dose per institutional guidelines.

Busulfan will be administered as an IV infusion over 2 hours every 6 hours following dose, administration and pharmacokinetic monitoring per University Of Minnesota institutional guidelines (MT2003-19S). Refer to guidelines to consider obesity dosing adjustment.

Standard Busulfan q6h Dosing Nomogram	
ABW	Dose
≤ 12 kgs	1.1 mg/kg/dose IV every 6 hours
> 12 kgs	0.8 mg/kg/dose IV every 6 hours

Cyclophosphamide will be administered as a 2 hour intravenous infusion with a high volume fluid flush and mesna per institutional guidelines on days -3 and -2.

Dosing is based on Actual Body Weight (ABW) unless ABW > 150% above Ideal Body Weight (IBW), in which case the dose should be computed using adjusted body weight. Refer to Cyclophosphamide Pharmacy Guidelines for calculating IBW based on age.

Antithymocyte Globulin (Atgam -equine) will be administered to umbilical cord blood recipients only at a dose of 30 mg/kg/dose IV every 24 hours on days -3, -2, and -1. Methylprednisone 1 mg/kg (no max dosing) IV will be administered prior to each dose of ATG. Additional steroids and/or other medications may be used as needed per the discretion of the treating physician. ATG will be administered per institutional guidelines.

5.2 GVHD Prophylaxis

Standard acute GVHD prophylaxis or, if eligible, an alternative GVHD prophylaxis will be used.

5.2.1 Tacrolimus

All patients (regardless of allograft source) will receive tacrolimus therapy beginning on day –3.

Tacrolimus dosing will be monitored and altered as clinically appropriate per institutional pharmacy guidelines. Dose adjustments will be made on the basis of toxicity and/or low tacrolimus levels.

Tacrolimus taper begins at day +100 for matched sibling donor (MSD) recipients, and day +180 for non-MSD recipients. Taper to zero by 10% weekly dose reduction over approximately 10 weeks.

5.2.2 Mycophenolate Mofetil (MMF)

All patients will begin mycophenolate mofetil (MMF) on day -3 at a dose of 15mg/kg/dose (max 1gm) IV q8h. Adult patients may be dosed at 1 gm IV q8h or 1.5 gm IV q12h (3 grams/day)

MMF dosing will be monitored and altered as clinically appropriate based on institutional guidelines. Patients will be eligible for MMF dosing and pharmacokinetics studies.
Use IV route between days –3 and +5, then, if tolerated, may change to PO between days +6 and +30.

Stop MMF at day +30 *or* 7 days after engraftment, whichever day is later, if no acute GVHD. (Definition of engraftment is 1st day of 3 consecutive days of absolute neutrophil count [ANC] $\geq$ 0.5 x 10^9 /L).

If there is no donor engraftment, do not stop MMF. If no evidence of donor engraftment on the day +21 bone marrow biopsy, notify URD search coordinator to pursue back-up UCB and arrange day +28 bone marrow biopsy according the institutional policy for management of slow engraftment.

If the patient has acute GVHD requiring systemic therapy, MMF may be stopped 7 days after initiation of systemic therapy for acute GVHD (e.g. resolution of skin rash, vomiting, and diarrhea).

5.3 Stem Cell Procurement

Acceptable stem cell sources include: HLA-matched related or unrelated donor bone marrow (6/6 or 5/6 antigen match) and related or single or double unrelated donor umbilical cord blood (6/6, 5/6 or 4/6 match). HLA-match is determined by serology for class I antigens (HLA A, B) and high resolution DNA typing for class II (DRB1) unless parental typing is available (DR is satisfactory).

5.3.1 Bone Marrow

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

Related donor BM will be collected according to current institutional guidelines.

A minimum of 2 x 10^8 nc/kg bone marrow cells.

No processing or manipulation of the donor marrow cells will be performed.

5.3.2 Peripheral Blood Stem Cells

A target of 5 x 10^6/kg and a minimum of 4 x 10^6 CD34+ cells/kg recipient weight will be collected by mobilized donor apheresis.

Day 0 for stem cell infusion may be shifted to day +1 or day +2 to move donor collections to weekdays or to accommodate a third donor collection, if needed. All associated procedures (i.e. G-CSF doses etc.) will shift accordingly.

Guideline for mobilized apheresis:

Day	Donor:
-5	G-CSF 16 mcg/kg SQ
-4	G-CSF 16 mcg/kg SQ
-3	G-CSF 16 mcg/kg SQ
-2	G-CSF 16 mcg/kg SQ
-1	G-CSF 16 mcg/kg SQ apheresis
0	G-CSF 16 mcg/kg SQ apheresis
+1	If necessary to achieve targeted cell dose G-CSF 16 mcg/kg SQ apheresis

Acetaminophen 15mg/kg/dose (max 650 mg) PO should be given 30 minutes before the first dose of G-CSF and continue every 8-12 hours for the duration of G-CSF administration.

Donors may experience any of the following side effects from G-CSF: bone pain, headaches, body ache, fatigue, nausea/vomiting, insomnia, dyspnea, rash, edema or other complaints. Donors experiencing intolerable symptoms (≥ grade 3 CTCAE v 4) attributed to G-CSF therapy should receive a dose reduction to 10 mcg/kg/dose.

Mobilized Donor Apheresis

Donors will undergo mobilized peripheral blood progenitor cell (PBPC) apheresis on days –1 and day 0 per institutional guidelines.

In most cases the target graft cell dose will be recovered in two aphereses; however, rarely a third apheresis may be

required the following day to achieve the minimum cell dose. More than 3 collections are not allowed.

5.3.3 Umbilical Cord Blood

Umbilical cord blood selection will be per the current University of Minnesota Cord Blood Unit Selection algorithm. One or two units may be used to obtain the minimum cell dose. There will be no processing of the cells.

Note: Unlicensed UCB units will be covered by University of Minnesota IND BB 14797 (C. Brunstein, MD, PhD – sponsor/investigator) and therefore will be in compliance with mandatory reporting to the FDA for minimally manipulated UCB units.

5.4 Stem Cell Infusion (day 0)

On day 0 the stem cells will be infused per cell source specific institutional guidelines.

Recommended premedication: acetaminophen 15mg/kg/dose (max 650 mg) PO and diphenhydramine 0.5 mg/kg/dose (max 25 mg) PO/IV.

Vital signs will be checked before and after the infusion, and one hour post infusion per University Of Minnesota transplant guidelines. More frequent vital signs may be required depending on reactions to the product infusion. Notify the resident physician immediately if patient exhibits signs or symptoms of a reaction.

5.5 Post-Transplant G-CSF (filgrastim)

Beginning on day +1, patients will receive G-CSF IV 5 micrograms/kg once daily and continuing once daily until the ANC is >2500 $x10^9$/L for 3 consecutive days.

G-CSF will be restarted at 5 mcg/kg/day (Max 480mcg/dose) IV if the ANC falls below 1000 $x10^9$/L or per institutional guidelines.

5.6 Expected Treatment Related Toxicity

Refer to appendix II.

5.7 Supportive Care

Patients will receive standard supportive transplant care, including antibacterial/antifungal/antiviral prophylaxis according to institutional guidelines or as modified based on clinical parameters.

Patients will be eligible for any supportive care studies regarding infectious disease prophylaxis and management, immunoglobulin support, etc. as appropriate.

5.8 Follow-Up

Follow-up will be according to the current University Of Minnesota BMT guidelines.

6.0 Drug Procurement

The preparative drugs (cyclophosphamide and busulfan) and supportive care drugs referenced in this study are standard of care, commercially available and will be administered according to current institutional guidelines.

7.0 Clinical Evaluations

All clinical evaluations are standard of care and will be done according to current institutional guidelines. Scheduled evaluations before day 30 may be performed (+/-3 days) from the targeted date; assessments to be performed on day 60 and 100 may be done on (+/-) 7 days of the targeted date; assessments on day 180, 1 year, 2 years and 3 years may be performed (+/- 30) days of the targeted date. In addition, targeted days may be altered as clinically appropriate.

	Pre-BMT work-up	During Preparative Regimen	Day 0	Day 1 to engraftment[1]	Follow-up Days 31-100	Follow-up per U of MN BMT guidelines
Written consent	X					
Medical history	X			daily		
Physical exam	X			daily	weekly	
Performance status	X				Day 100	
Weight	X		X	X(3)		
Height	X					
GVHD evaluation				daily	weekly	
CMV Surveillance				weekly	weekly	prn
EBV Surveillance				every other week	every other week	
CBC, diff, platelet	X	daily		daily	weekly	
PT/PTT	X					
Alk phos, AST, ALT, tot bili	X	weekly		weekly		
Creat, BUN, Na, K, CO2	X	daily	daily	daily	weekly	
Pre-BMT viral panel	X					
Urinalysis	X					
Pregnancy test (FOCBP)	X					
BM bx/asp	X			Day 21	Day 60, 100	6 and12 months
Chimerism – BM	X			Day 21	Day 60, 100	6 and12 months
Chimerism – PB	X			Day 28	Day 100	6 and12 months
EKG	X					
MUGA or echo	X					
Chest x-ray or CT	X					
PFT's	X					
Disease eval	X			Day 21	Day 100	X

1 -engraftment defined as absolute neutrophil count (ANC) is >2500 $x10^9$/L for 3 consecutive measurements

8.0 Event Reporting

This is a treatment guideline to allow routine clinical data to be collected and maintained in OnCore and the University Of Minnesota Blood and Marrow Database as part of the historical database maintained by the department. The only research element is the collection of routine clinical data in association with study milestones. Therefore, the only events reportable to the University Of Minnesota Institutional Review Board in a prompt manner (within 5 business days of discovering the event) will be those in association with data collection. Primarily these risks would be:

- Any breach in confidentiality that may involve risk to the subject or others *in association with the data collection*
- Any complaint *in association with the data collection* of a subject that cannot be resolved by the research staff

Any report should be made using the Report form found on the IRB's website (http://www.research.umn.edu/irb/).

9.0 Study Data Collection and Statistical Plan

Specific transplant related endpoints include:

- Days to ANC engraftment
- Incidence of engraftment failure at day 42
- Incidence of acute GVHD at 100 days
- Incidence of chronic GVHD at 6 months and 1 year
- Incidence of transplant related mortality (TRM) at 6 months and 1 year
- Incidence of relapse at 1 year and 2 years
- Disease free survival at 2 year, 5 year and 10 years
- Overall survival at 2 year, 5 year and 10 years

All endpoint data will be recorded in the University of Minnesota Blood and Bone Marrow Database as part of the historical database maintained by the department.

9.1 Trial Size Justification

The primary objective is to record outcomes and patient characteristics in the BMT database for patients using partially matched unrelated or related donors or umbilical cord blood as a cell source and are treated in a standard manner. Based on prior a prior study (MT2000-12), enrollment will be minimal as other transplant approaches and higher priority clinical trials limit accrual for this transplant study. However, this study remains necessary for selected patient populations who lack a histocompatible related

donor and have no more promising treatment option. No trial size justification is needed.

9.2 Enrollment Plan

We plan to enroll 2-3 per year.

9.3 Analysis of Primary and Secondary Endpoints

Cumulative incidence will be used to estimate TRM, Relapse, neutrophil engraftment, GVHD and engraftment failure treating non-events as competing risks. Kaplan-Meier curves will be used to estimate disease-free survival and overall survival.

9.4 Safety Monitoring

We have studied the regimen for patients with these diagnoses for the past 12 years and it has been shown to be safe. Continuous stopping rules are no long needed. Safety parameters will be monitored on a yearly basis.

Appendix I – Performance Status Scales

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

LANSKY PLAY PERFORMANCE STATUS SCALE

Percentage	
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

REFERENCE
Lansky SB, List MA, Lansky LL, Ritter-Sterr C, Miller DR (1987). "The measurement of performance in childhood cancer patients". Cancer 60 (7): 1651–6.

Appendix II – Expected Toxicities Of The Preparative Regimen And Transplantation

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

Cyclophosphamide		
Common	**Less Common**	**Rare**
• 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	• low platelet count with increased risk of bleeding • darkening of nail beds • acne • tiredness • infection • fetal changes if pregnancy occurs during cyclophosphamide	• 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) (umbilical cord blood recipients only)		
Common	**Less Frequent**	**Uncommon**
• fever • chills • low white blood cell count with increased risk of infection • pain • headache • abdominal pain • diarrhea • hypertension • nausea • low platelet count with increased risk of bleeding • peripheral edema • dyspnea • asthenia • hyperkalemia • tachycardia	• malaise • dizziness	• severe allergic reaction (anaphylaxis)

GVHD Prophylaxis

Mycophenolate mofetil (MMF)		
Common	**Less Common**	**Rare, but may be serious**
• miscarriage • birth defects • diarrhea • damage to unborn baby • limited effectiveness of birth control • stomach pain • upset stomach • vomiting • headache • tremors • low white blood cell count with increased risk of infection • increased blood cholesterols • swelling of the hands, feet, ankles or lower legs	• anemia • rash • difficulty falling asleep or staying asleep • dizziness • uncontrollable hand shakes	• difficulty breathing • unusual bruising • fast heartbeat • excessive tiredness • weakness • blood in stool • bloody vomit • change in vision • secondary cancers, such as lymphoproliferative disease or lymphoma • Progressive Multifocal Leukoencephalopathy

Tacrolimus (FK506, Prograf®)

Common occurs in more than 20% of patients	**Less Common** occurs in 5 to 20% of patients	**Rare** occurs in fewer than 5% of patients

▪ Kidney problems ▪ Loss of magnesium, calcium, potassium ▪ Cardiovascular: hypertension ▪ Tremors ▪ hyperlipidemia ▪ thrombocytopenia ▪ Infections	▪ Nausea ▪ Vomiting ▪ Liver problems ▪ Changes in how clearly one can think ▪ Insomnia ▪ Unwanted hair growth ▪ Confusion	▪ Seizures ▪ Changes in vision ▪ Dizziness ▪ microangiopathic hemolytic anemia ▪ post-transplant lymphoproliferative disorders

It is very important that grapefruit or drinks with grapefruit juice are not consumed while taking Tacrolimus. Grapefruit has an ingredient called bergamottin, which can affect some of the treatment drugs used in this study. Common soft drinks that have bergamottin are Fresca, Squirt, and Sunny Delight.

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		
Common	**Less Common**	**Rare**
• none	• bone and muscle pain • abnormal blood tests which suggest that the drug is affecting the liver	• fast heartbeat • low blood pressure • allergic reaction (may include shortness of breath, wheezing, swelling in the mouth or throat, hives, itching, flushing, or fever)