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DMS 13179: A Prospective Randomized Trial Examining Low- or Intermediate-Dose Cyclophosphamide for Hematopoietic Stem Cell Mobilization in Patients with a Hematologic Malignancy

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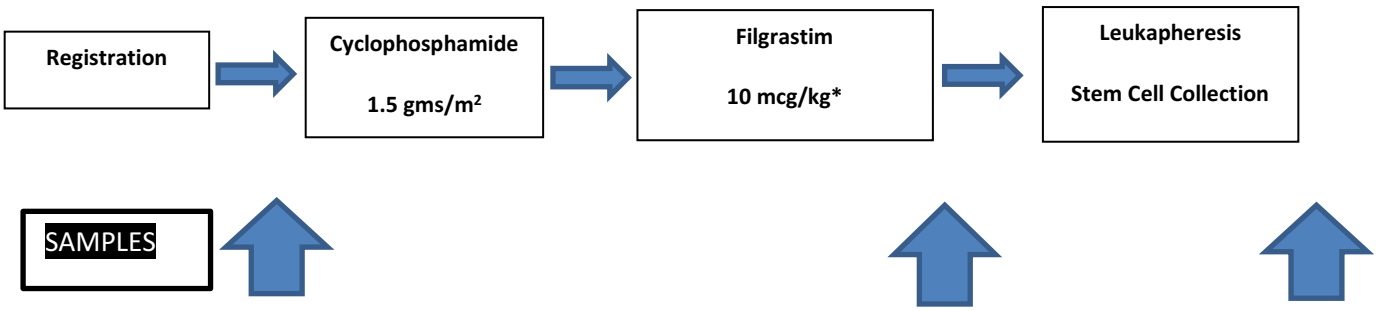
PRE-TREATMENT EVALUATION

For a patient to be approved for this mobilization trial, the patient must be cleared for transplantation by the Transplant Attending, using the standard required results ("Pre-Transplant SOP Evaluation – BMT SOP 0023"). The following are the eligibility criteria for this trial:

	Pretreatment	**Leukapheresis**	**Transplant Course**
Patient approved for transplant (see above)	X		
Laboratory analysis – to include blood sample pre-mobilization, one sample from the mobilized cell product and one sample around Day 15 following transplant	X	X First day of collection	X
Engraftment (neutrophils and platelets)			X

TREATMENT SCHEMA FOR MOBILIZATION

For the additional 13 non-randomized subjects, each patient will be placed on cyclophosphamide 1.5 gms/m2.



1.) Samples will be obtained at baseline/pre-treatment (blood), on the first day of collection (mobilized progenitor cells) and a final blood sample at the time of bone marrow recovery (engraftment) following transplant, approximately day 15 following transplant.

2.) G-CSF dose will be based on National Marrow Donor Program guidelines

1. 1.0 INTRODUCTION

1.1. ***Current treatment for patients with myeloma***

1.1.1. The current treatment for myeloma patients includes 3 to 4 cycles of therapy to achieve cytoreduction and then proceed onto autologous stem cell collection and a stem cell transplant (**1**). Prior to an autologous stem cell transplant, patients must have their peripheral blood stem cells collected, so the cells can be re-administered following high dose chemotherapy. The process of stimulating and releasing bone marrow cells into the blood for collection is called mobilization.

1.1.2. The optimal method to mobilize autologous stem cells for patients with myeloma is not known (**2**). Autologous stem cells can be "mobilized" using a growth factor alone or a combination of a growth factor with a chemotherapy medication. Numerous trials have demonstrated that the administration of chemotherapy with a growth factor**,** called granulocyte-colony stimulating factor or filgrastim**,** yields more cells than using filgrastim alone (**3,4**). Cyclophosphamide is the most common chemotherapy agent used for mobilization, in combination with filgrastim (**5**) Cyclophosphamide is an appealing agent since it demonstrates clinical activity against myeloma cells and it may provide *in vivo* purging of residual myeloma cells (**6**). In addition, the combination of cyclophosphamide and filgrastim work synergistically to mobilize autologous stem cells (**2,7**). A multi - center analysis of transplant centers using the Center for International Blood and Marrow Transplant (CIBMTR) database indicates that the combination of cyclophosphamide with filgrastim resulted in an increased number of cells collected, a fewer number of apheresis required and a fewer number of patients failing to mobilize, when compared to filgrastim alone (**5**). Unfortunately, when cyclophosphamide is added to filgrastim in a mobilization regimen, there is increased risk for febrile neutropenia and an increased incidence of side effects (**8, 9**).

1.1.3. In addition to the mobilization regimen, patient characteristics and a patient's clinical course may also determine a patient's ability to mobilize autologous stem cells. In particular, collections of a low number of CD34+ cells can be due to the patient's age, prior radiation therapy, prior use of thalidomide or lenalidomide or the use of single-agent filgrastim for mobilization. The standard international minimal number of CD 34+ cells/kg of body weight recommended for an autologous stem cell transplant is 2 x 10^6 CD34+ cells/kg (**1-4**). The term "mobilization failure" refers to an inadequate collection of CD34+ cells needed for an autologous stem cell transplant. This definition is based on the absolute number of CD34+ cells collected or the inability to collect a specified number of cells in a certain number of leukapheresis. Mobilization failure can also be predicted by the number of CD34+ cells mobilized into the peripheral blood following the mobilization treatment regimen. If the number of CD34+ cells in the blood is low, the apheresis process will not collect enough cells." **(10-14).** Mobilization failure rates for myeloma patients vary, based on how "failure" is defined. For example, the Transplant Team at Memorial Sloane Kettering Cancer Center noted that 13% of myeloma patients failed to mobilize cells. This group defined "failure" as the inability to collect 5 x 10^6 CD34+cells/kg, a number that is much higher than the international standard number

of CD34+ cells required (2 x 10^6 CD34+ cells/kg). The general consensus is a mobilization failure rate of 5% to 13% in myeloma patients (**1-4, 10**).

1.2. ***Defining the optimal cyclophosphamide dose for mobilization - Review of the literature on mobilization in multiple myeloma***

1.2.1. No prospective randomized trials have evaluated the optimal dose of cyclophosphamide to mobilize autologous stem cells (**1,2,15**). Published reports include retrospective analyses, with the doses of cyclophosphamide ranging from 1.5 gms/m^2 to 7 gms/m^2 (**1-5,14,16**). Historically, higher doses of cyclophosphamide (5 gms/m^2 to 7 gms/m^2) were used in the early 2000's (**9**). The literature indicates that the higher the cyclophosphamide dose, the greater the toxicities, but the greater the number of cells mobilized and collected. Weighing these two conflicting issues, over the past 5 years, transplant centers have been administering lower doses of cyclophosphamide (doses between 1.5 to 5 gms/m^2) for mobilization, in an attempt to achieve maximal cell yield with fewer side effects (**17-19**).

1.2.2. A single center retrospective analysis of two mobilization regimens compared low dose (1 to 2 gms/m^2) with intermediate dose (3 to 4 gms/m^2) cyclophosphamide in combination with filgrastim. Both groups of patients mobilized an adequate number of cells for transplantation (89% of patients in the low dose arm compared with 92% of patients in the intermediate dose arm), but the incidence of febrile neutropenia was three times higher in the intermediate dose arm (38% versus 13%) (**17**). Another retrospective analysis compared two doses of cyclophosphamide, either 2 gms/m^2 or 4 gms/m^2, with filgrastim. There was a significant increase in the number of hospital admissions for febrile neutropenia in the patients receiving the higher dose of cyclophosphamide, when compared to the lower dose ($p = 0.0005$). Mobilization failure occurred in 6% of patients in the higher dose as compared with 11% of patients in the lower dose arm. Of the five patients that did not mobilize in the lower dose arm, four patients mobilized with a subsequent attempt (**19**). Finally, a recent trial compared mobilizing myeloma patients using low dose cyclophosphamide (1.5 gms/m^2) and filgrastim with a new mobilizing CXCR4 antagonist, called Plerixafor. Six patients (8.1%) in the cyclophosphamide group failed to mobilize cells (**20**).

1.2.3. In summary, doses of cyclophosphamide have been used ranging from 1.5 gms/m^2 to 7 gms/m^2. The mobilization failure rate in myeloma patients ranges between 5% and 13%.When used in combination with filgrastim, higher doses of cyclophosphamide mobilize a larger number of CD34+ cells, at the expense of increased toxicity, side effects and hospital admissions for febrile neutropenia. **(15-20**).

1.2.4. The *International Myeloma Working Group* recently reviewed various mobilization regimens used for myeloma patients. (**1,3,4**). The Committee concluded that the combination of cyclophosphamide and filgrastim mobilized more cells when compared to filgrastim alone, but the optimal dose of cyclophosphamide was not known. The Committee recommended exploring lower doses of cyclophosphamide, and not exceeding doses of 4 gms/m^2**.** In addition, the group recommended pursuing novel manners to mobilize cells, including ways to improve efficacy and decreasing costs. (**3**)

1.2.5. The trial is designed as a non-inferiority trial. If the lower dose arm is shown to be non inferior, this will be a **major** new finding that will change clinical practice here at Dartmouth and other transplant centers. As a result, if the lower dose is shown to be non-inferior, additional patients will be accrued to this arm to confirm the findings and to address possible superiority of the lower dose arm. The number of patients needed will be based on the preliminary results.

1.2.6. Since the results of the trial demonstrated no difference between the two doses of cyclophosphamide in terms of number of CD34+cells/kg collected, 13 additional patients will be accrued to the lower dose arm (1.5 gms/m2). These additional patients will be combined with the results from the other participants previously treated on the low dose arm and compared as a group with the high dose arm. (Please refer to Statistical Considerations – Section 13, for details).

2.0 OBJECTIVES

2.1 Primary Objective

2.1.2 The primary objective of this clinical trial is to determine if a lower dose of cyclophosphamide combined with filgrastim can mobilize an adequate number of CD34+ progenitor cells with less toxicity.

We postulate that low dose cyclophosphamide mobilization (1.5 gms/m^2) will be as efficacious as the intermediate dose (3 gms/m^2).

2.1.3 To define the primary objective, we will identify the number and types of cells collected within the apheresis products and characterize the details of the apheresis process. In particular, we will define the following:

- The number of peripheral blood CD34+ cells identified on Day 1 of collection
- The number of apheresis required to collect >/= 5 x 10^6 CD34+cells/kg for myeloma patients and >/= 3 x 10^6 CD34+cells/kg for NHL patients. (These numbers represent a "goal" and not a stopping criteria).
- The number of cells collected (MNC/kg and CD34+cells/kg)
- Failure to mobilize will be defined as:
    - < 1x10^6 CD34+cells/kg collected after 2 days of apheresis OR
    - Failure to mobilize an adequate number of CD34+ progenitor cells
        - Blood CD34+ cell number < 5 cells/mcl if weight ≤ 75kg
        - Blood CD34+ cell number < 10 cells/mcl if weight > 75kg
- Toxicities during the mobilization and apheresis processes

2.1.3 If the lower dose arm demonstrates non-inferiority at completion of patient accrual, then additional patients will be added to the lower dose arm to confirm non-inferiority or superiority. The number of patients needed to answer this will be based on statistical evaluation of the preliminary results (see Statistical Analysis).

2.2 Secondary Objectives

2.2.1 Define resource utilization during the mobilization and apheresis processes:

- Transfusions of red blood cells
- Transfusion of platelets
- Hospitalizations
- Incidence of febrile neutropenia

2.3 Exploratory Objectives

2.3.1 Determine the post-transplant engraftment of neutrophils and platelets.

2.3.2 Qualitative and quantitative analyses of mobilized lymphocytes (Elective-pending funding).

3.0 ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

3.1.1 All patients must have a pathologic diagnosis of one of the following malignancies:

- Non-Hodgkin's Lymphoma, including B- and T-cell lymphoma
- Multiple Myeloma or another plasma cell dyscrasia (Waldenstrom, Amyloidosis)

3.1.2 The patient must be approved for transplant by the treating Transplant physician. This includes completion of their pre-transplant workup, as directed by standard DHMC SOPs (BMT SOPs 0023 and 0025 - Appendix).

3.1.3 This must be the patient's FIRST mobilization attempt.

3.1.4 Patients are eligible if an autologous transplant is planned within approximately 12 months from the time of collection of cells.

3.1.5 Prior Treatment: No previous cytotoxic chemotherapy within 4 weeks prior to initiation of therapy. (This does not include IMIDs, proteasome inhibitors, monoclonal antibodies or steroids.)

3.1.6 No radiation within 4 weeks of mobilization attempt.

3.1.7 Age $\geq$18, and $\leq$ 75 years

3.1.8 No significant co-morbid medical or psychiatric illness that would significantly compromise the patient's clinical care and chances of survival.

3.1.9 Informed consent must be signed prior to the treatment. Patients must willingly consent after being informed of the procedure to be followed, the nature of the therapy, alternatives, potential benefits, side effects, risks and discomforts. (Human protection committee approval of this protocol and a consent form is required.)

3.2 Exclusion Criteria

3.2.1 Medical, social, or psychological factors that would prevent the patient from receiving or cooperating with the full course of therapy.

3.2.2 Documented hypersensitivity to any of the drugs used in the protocol.

4.0 REGISTRATION AND DATA SUBMISSION

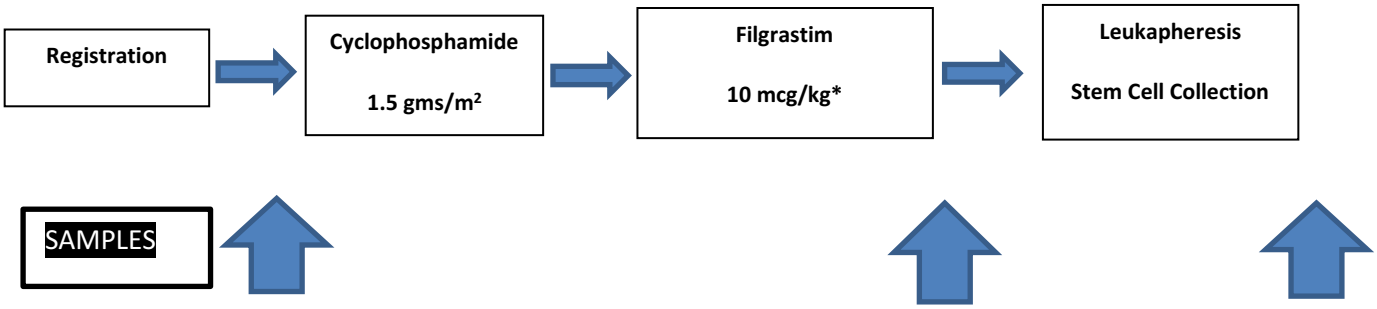
This is a randomized trial using two standard doses of cyclophosphamide, with a standard dose of filgrastim. To enter eligible patients or to discuss a patient's eligibility, please contact Dr. Kenneth R. Meehan (or any of the Transplant physicians) at 603-650-4628 or the Clinical Research Associate (Bridget Labrie at 603-650-6227). Informed consent must be signed prior to the initiation of treatment.

5.0 GENERAL WORKUP AND DIAGNOSTIC PROCEDURES

Since this treatment regimen offers standard of care therapy, no additional workup or evaluation is needed besides the tests required as a standard part of the pre-transplant evaluation, as listed in SOPs (BMT SOPs 0023 and 0025 - Appendix).

5.1 Informed Consent: Patients must willingly consent after being informed of the procedure to be followed, the nature of the therapy, alternatives, potential benefits, side effects, risks and discomforts. (Human protection committee approval of this protocol and a consent form is required.)

5.2 **TREATMENT SCHEMA FOR MOBILIZATION (Table 1)**



1.) Samples will be obtained at baseline/pre-treatment (blood), on the first day of collection (mobilized progenitor cells) and a final blood sample at the time of bone marrow recovery (engraftment) following transplant, approximately day 15 following transplant.

2.) G-CSF dose will be based on National Marrow Donor Program guidelines

******For the remaining patients, each patient will be placed on cyclophosphamide 1.5 gms/m2 arm and will NOT be randomized.**

6.0 RANDOMIZATION and TREATMENT PLAN

6.1 Patients will be randomized based on age (> 60 years, <60 years) and duration of lenalidomide use (> 4 months, < 4 months) using a randomization process within Micorsoft Excel, developed by Dr. Jiang, the study statistician. Patients will be randomized to either 1.5 gms/m^2 or 3 gms/m^2 after signing an informed consent.

Randomization will be based on:

- Diagnosis (NHL vs. Myeloma)

- Age (≤ or > 60 years)
- Prior radiation (yes or no)
- Prior therapy (≤ or > 2 prior treatments)
- For myeloma patients, ≤ or > 4 months of prior lenalidomide or thalidomide therapy
- Platelet count (≤ or > 100,000/mcl)
- As noted previously, randomization will not be used once the preliminary data have been analyzed and if the lower dose arm demonstrated non-inferiority. Subsequent patients will be treated on the lower dose arm.

6.2 **Cyclophosphamide**

After randomization, patients will receive either 1.5 gms/m^2 or 3 gms/m^2 (based on actual BSA). The schedule and the administration of cyclophosphamide and filgrastim will follow the DHMC SOP (BMT SOP 0025: Stem Cell Mobilization Protocol- Appendix). The administration of cyclophosphamide is outlined in the SOP. If clinically indicated, patients may receive intravenous mesna (600 mg/m^2) 15 minutes prior to cyclophosphamide and again at 4 and 8 hours afterwards. Each infusion will be given over 15 minutes. Oral mesna can be substituted for the two post-cyclophosphamide doses. Oral mesna (1200 mg/m^2) will be administered at 2 and 6 hours after the start of cyclophosphamide. Cyclophosphamide will be administered intravenously over one hour.

For the convenience of participant, the infusion of cyclophosphamide may be administered locally by their primary hematologist. The completed orders will be provided by DHMC-Lebanon to the study participant's local facility (including local pharmacy) for the single treatment dose of cyclophosphamide and subsequent doses of filgrastim. The evaluation of each study participant, data supervision and management, toxicity management, and adverse event reporting will all occur at DHMC – Lebanon. Any significant impediments to treatment on a clinic day should immediately be reported by the local facility to the DHMC – Lebanon research team.

6.3 **Zarxio** - (filgrastim-sndz),

Zarxio (Sandoz, Inc.) is biosimilar to Amgen Inc.'s Neupogen (filgrastim). Zarxio is an FDA-approved biosimilar product. A biosimilar product is a compound that is approved based on clinical data demonstrating efficacy to a similar to an already-approved product, known as a reference product. The biosimilar shows no clinically meaningful differences in toxicity, safety or effectiveness from the reference product. Only minor differences are allowable in biosimilar products. Zarxio is approved for the same indications as Neupogen (filgrastim), and can be prescribed for patients undergoing autologous peripheral blood progenitor cell collection. The dosing of Zarxio is the same as Filgrastim (outlined below).

6.4 **Filgrastim**

A standard dose and schedule of filgrastim will be used. Approximately 48 hours after cyclophosphamide, filgrastim (using NMDP guidelines below) will be administered as a daily subcutaneous injection until completion of collection (BMT SOP 0025). Complete blood counts (CBC) will be monitored approximately 3x/week and the dose of filgrastim adjusted, according

to the CBC results. Filgrastim will continue until completion of leukapheresis. The following NMDP guidelines will be used for dosing filgrastim, based on patient's weight and vial size.

Donor weight (Kg)	Vial size:300 mcg	Vial size : 480 mcg	Daily dose (mcg/day)
45 to 60	2	0	600
61 to 78	1	1	780
79 to 90	3	0	900
91 to 96	0	2	960
97 to 108	2	1	1080
109 and greater	4	0	1200

6.5 **Leukapheresis**

We previously demonstrated that the time to collection of autologous hematopoietic stem cells is 10-12 days following cyclophosphamide and daily filgrastim (**21**). Patients will undergo peripheral blood stem cell harvesting via leukapheresis, depending upon the peripheral blood WBC and CD34+ cell count, generally between Days 10 and 12, following cyclophosphamide. After the combination of cyclophosphamide and G-CSF are administered, there is a typical clinical course marked by a decrease in blood counts within 3 days and a sudden rise in CBC, most strikingly in the WBC, between days 10 to 12 following cyclophosphamide administration. Based on this clinical course, peripheral blood CD34+ cell numbers will be examined (as a marker of circulating stem cells), beginning Day 10, based on a patient's CBC recovery. Apheresis will begin once the blood CD34+ number reaches approximately 10 cells/mcl.

The collection process will be standard for each patient on trial. This will be accomplished by determining the number of cells collected each day (CD34+ cells and MNC) per volume of blood processed.

The goal for collection will be the following:
Patients will receive consecutive days of leukapheresis until $\geq$ 5 x 10^6 CD34+cells/kg for myeloma patients and $\geq$ 3 x 10^6 CD34+cells/kg for NHL patients have been collected. (See Section "How to handle poor mobilizers" below.)

Peripheral blood stem cells will be cryopreserved in the usual manner, per the Cell Processing Laboratory protocol.

If < 1 x 10^6 CD34+cell/kg has been obtained after 2 days of leukaphereses, leukapheresis will be discontinued and this patient will be removed from protocol, since this is one endpoint of the trial. In addition, failure to mobilize cells will be defined as a peripheral blood CD34+ cell number < 5 cells/mcl if patient's weight $\leq$ 75kg or a blood CD34+ cell number < 10 cells/mcl if patient's weight > 75kg.

6.5 How to handle "Poor Mobilizers"

Poor mobilizers are defined as patients who sluggishly mobilize autologous blood stem cells but do not meet criteria for "removal from trial". Typically, these patients mobilize enough cells for transplant but do not meet the target CD34+ cell number. These patients will NOT be removed from trial. Apheresis can be discontinued in these patients before reaching the target CD34+ cell number if, at the discretion of the treating physician or the PI, it is not clinically

indicated to continue collection of cells, since this may be putting the patient at increased risk and enough cells have been obtained for transplantation. The patient will remain on protocol and will be considered evaluable on an "intent to treat" analysis. These patients will be defined as "poor mobilizers'' within the database.

In contrast, if a patient does not meet these end point collection criteria or if another day of collection is not clinically indicated but a patient has not met the CD34+ cell collection criteria, the collection process can be terminated at the discretion of the PI and treating physician. For example, a myeloma patient mobilizes 4.8 x 10^6 CD34+cells/kg on the first day). The patient will remain on protocol and will be considered evaluable on an "intent to treat" analysis.

6.6 **Supportive Medications**

Following cyclophosphamide administration, once the patient's absolute neutrophil count drops to $\leq$ 500 cells/mcl, oral prophylactic fluconazole (400 mg/day), acyclovir (800 mg BID) and levaquin (750 mg/d) will be started, if the patient is not already taking these medications.

6.7 **Peripheral Blood Stem Cell (PBSC) Collection and Storage**

The collection, concentration and storage of PBSC will be standard for all patients. Briefly, a 4-blood volume leukaphereses PBSC collection will be performed daily using a COBE Spectra cell separator (COBE BCT, Lakewood, CO). Collected cells will be concentrated to 50 – 100 ml in a refrigerated centrifuge. PBSC concentrates will be cryopreserved in a medium consisting of 6% low molecular weight hydroxyethyl starch (Normosol-R pH 7.4, Abbott Laboratories, North Chicago, IL.), 10% dimethyl sulfoxide (DMSO) (Cryoserv, Research Industries, Salt Lake City, UT), and autologous serum albumin, 20% concentration. Cells will be frozen in Cryocyte freezing bags (Nexell Therapeutics Inc) in a controlled rate freezer (Custom BioGenic Systems, Shelby Township, MI). At the conclusion of this freezing, the cells will be transferred to the vapor phase of a monitored liquid nitrogen freezer (CryoPlus III, Forma Scientific, Marietta, OH) at a temperature of –120 ^{0}C or below.

Pregnancy Risks: The risks of the drugs and procedures used in this study to a pregnancy are unknown. Pregnant women may not take part in this research study. All women who could become pregnant will have a pregnancy test. Men taking part should not father a baby while on this study. All men and women who could become pregnant will be required to use a medically approved method of birth control in order to take part in this research study.

7.0 POTENTIAL TOXICITIESAND MANAGEMENT

7.1 Evaluation of toxicities (other than Hematologic) will be graded using NCI Common Toxicity Criteria, specifically CTC AE 4.0. Life-threatening toxicities must be reported to the principal investigator, the clinical research assistant and the IRB. The following laboratory test result abnormalities and adverse events should be captured on the non-serious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

- Any laboratory test result/adverse reaction that is $\geq$ Grade 4 or meets the definition of an SAE
- Any laboratory test result/adverse reaction abnormality that required the subject to have study drug discontinued or interrupted

- Any laboratory test result/adverse reaction deemed related to the treatment that required medical intervention, either by requiring an office/infusion room visit, treatment (ranging from medication administration, hydration or transfusion).

Monitoring of toxicities will terminate on the last day of collection, since treatment-related toxicities occur during this time period. Patients who complete mobilization will be considered "off treatment" on the date of the last mobilization. There will be no specified follow up beyond the off treatment period other than following for engraftment. However, should any life threatening event directly linked to the study take place within 2 weeks post-mobilization, the investigator shall use his/her discretion in reporting the event to the appropriate committees.

7.2 Leukapheresis will be initiated approximately 11 - 12 days following cyclophosphamide administration. Patients will be monitored clinically for toxicities during the mobilization process until completion of collection of stem cells. In particular, the following will be monitored:

- Transfusions of red blood cells
- Transfusion of platelets
- Hospitalizations
- Incidence of febrile neutropenia

7.3 Engraftment of neutrophils and platelets will be determined following transplant. Standard definitions of engraftment will be used. Engraftment of each cell line will be defined as an absolute neutrophil count (ANC) of $\geq$ 500/mm^3 for three days (defined as first day) and a platelet count of 20,000/mm^3 un transfused (defined as first day). Standard definitions of engraftment are being used to allow comparisons to results within the literature.

8.0 DRUG FORMULATION, AVAILABILITY AND TOXICITY

8.1 **Cyclophosphamide**

8.2 **Mechanism of action:** Cyclophosphamide is a pro drug that requires activation. Following hepatic and cellular activation, phosphoramide mustard and acrolein are formed. Phosphoramide mustard is the alkylating agent that demonstrates cytotoxic effects. Acrolein binds to proteins but does not contribute to the anti-tumor effects.

8.3 **Toxicities***:* Potential toxicities include: fever and/or chills, nausea and vomiting, anemia, oliguria/anuria, diarrhea, mental status changes, sinus tachycardia, elevated bilirubin, thrombocytopenia, BUN elevation, serum creatinine elevation, elevated transaminase, elevated alkaline phosphatase, pulmonary congestion, fatigue/weakness/malaise, dyspnea, pruritus, edema, erythema leukopenia, stomatitis, anorexia, rash, infection, weight gain ($\geq$10%), arrhythmias, hypomagnesemia, acidosis, hypocalcemia, dizziness, dry skin, exfoliative dermatitis, GI bleeding, sensory dysfunction, jaundice, pulmonary edema, proteinuria, hypophosphatemia, headache, coagulation disorders. Acrolein is toxic to the bladder and is associated with the development of hemorrhagic cystitis.

8.4 **How supplied**: cyclophosphamide is commercially available

8.5 **Zarxio** (filgrastim-sndz; Sandoz, Inc.)

8.6 Zarxio (Sandoz, Inc.) is biosimilar to Amgen Inc.'s Neupogen (filgrastim). Zarxio is an FDA-approved biosimilar product. The dosing of Zarxio is the same as Filgrastim (outlined below).

8.7 **Mechanism of action**: The colony stimulating factors (CSFs) are a family of glycoprotein hormones that support survival, clonal expansion, and differentiation of hematopoietic progenitor cells. CSFs induce partially committed progenitor cells to divide and to differentiate in the granulocyte-macrophage pathways.

8.8 **Toxicities:** Nausea/vomiting, skeletal pain, alopecia, diarrhea, neutropenic fever, mucositis, fever, fatigue, anorexia, dyspnea, headache, cough, skin rash, chest pain, generalized weakness, sore throat, stomatitis, constipation, pain.

8.9 **How Supplied**: Zarxio is commercially available.

8.10 **Filgrastim** (Recombinant Human Granulocyte Colony Stimulating Factor; Amgen)

8.11 **Mechanism of action**: The colony stimulating factors (CSFs) are a family of glycoprotein hormones that support survival, clonal expansion, and differentiation of hematopoietic progenitor cells. CSFs induce partially committed progenitor cells to divide and to differentiate in the granulocyte-macrophage pathways.

8.12 **Toxicities:** Nausea/vomiting, skeletal pain, alopecia, diarrhea, neutropenic fever, mucositis, fever, fatigue, anorexia, dyspnea, headache, cough, skin rash, chest pain, generalized weakness, sore throat, stomatitis, constipation, pain.

8.13 **How Supplied**: Filgrastim is commercially available.

9.0 REQUIRED DATA and CORRELATIVE LABORATORY STUDIES

9.1 The required data is divided into four sections: 1) Pre-Treatment Evaluation; 2) Mobilization/Collection; 3) Post-transplant engraftment and 4) Evaluation of the Laboratory Correlates. The "Pre-Treatment Evaluation", the "Mobilization and Collection Evaluation" and "Post-transplant engraftment" will be monitored by the treating Transplant Team and the Clinical Research Assistant.

9.2 Pre-Treatment Evaluation**:** The "Treatment Evaluation" required for this trial is listed in Section 5.0, "General Workup and Diagnostic Procedures".

9.3 During the mobilization and collection processed, toxicity will be monitored (Section 7.0, "Potential Toxicities, Dose Modifications and Management").

9.4 We will identify the number and types of cells collected with the apheresis process, a process that is performed regularly for each transplant patient. The following data will be collected at the time of stem cell collection:

- The number of peripheral blood CD34+ cells on Day 1 of collection
- The number of apheresis required to collect $\geq$ 6 x 10^6 CD34+cells/kg of body weight
- The number of cells collected (MNC/kg and CD34+cells/kg)
- The number of patients who failed mobilization, defined as:
    - < 1x10^6 CD34+cells/kg collected after 2 days of apheresis
    - Failure to mobilize an adequate number of CD34+ progenitor cells
        - Blood CD34+ cell number < 5 cells/mcl if weight $\leq$ 75kg
        - Blood CD34+ cell number < 10 cells/mcl if weight > 75kg

9.5 Post-transplant engraftment of neutrophils and platelets.

Engraftment of each cell line will be defined as an absolute neutrophil count (ANC) of $\geq$ 500/mm^3 for three days (count first day)and a platelet count of 20,000/mm^3 un transfused (count first day). Standard definitions of engraftment are being used.

9.6 Evaluation of the Mobilized Cells

Pending budget issues, the following translational studies may be performed, comparing the results between the two cohorts:

- Phenotypic analyses of early progenitor cells
- Cytotoxicity of the mobilized effector cells
- CD3+ CD8+ NKG2D+ T cell cytotoxicity; Isolation of the cytotoxic effector cells
- Intracellular cytokine analysis of the mobilized effector cells

9.7 Patient Samples – pending funding, patient blood samples will be analyzed in the laboratory. Patient samples will be processed by the Immune Monitoring Laboratory. Each sample will be labeled with the trial number and provided with a unique patient number (UPN). No individual patient samples will be identifiable. The laboratory tests will be conducted by the Immune Monitoring Lab and a copy of the results will remain in the laboratory and with the PI. The PI will be the only individual with access to the UPN and patient identity so that lab results can be correlated with clinical outcomes.

9.7.1 Phenotypic analysis of early progenitor cells: The mobilized mononuclear cells will be analyzed to determine the presence of early progenitor cells. Patients' samples will include a baseline pre-leukapheresis blood sample and one sample from the leukapheresis product. Cell surface phenotype of the mononuclear cell (MNC) fraction of the peripheral blood and peripheral blood stem cells will be determined using appropriate fluorescein isothocyanate (FITC)- or phycoerythrin (PE)-conjugated monoclonal antibodies and three-color flow cytometry. "Early" hematopoietic stem cells may demonstrate the following expression of surface antigens: CD34+/CD33-, CD34+/CD38-, and CD34+/HLA-DR-. Samples of the collected mononuclear cells (MNC) cells will be labeled with conjugated monoclonal antibodies directed against the following antigens: CD34, CD33, CD38, HLA-DR, CD133, and CD90.

9.7.1.1 Significance of CD133 and CD90: CD133 is a recently recognized stem cell antigen that identifies earlier progenitor cells then those identified with CD34 antigen expression alone. CD133 is found on 50% of CD34-negative cells that contribute to long-term hematopoiesis, indicating that CD133 is likely an early marker of hematopoiesis. The presence of CD90 (also known as Thy-1) on progenitor cells is an excellent predictor of prolonged engraftment.

9.7.1.2 All flow cytometry data acquisition and automated analyses will be performed using two or three color staining on a FACSCalibur™ multipurpose flow cytometer and application-specific software (BDIS, San Jose, CA).

9.8 Phenotypic analysis of mobilized effector cells: Patients' samples will include a baseline pre-leukapheresis blood sample and one apheresis sample. Since we will be focusing on the mobilized effector cells with emphasis on the T cell population, the panel will contain antibodies directed against T cells (CD3), Helper T cells (CD3+/CD4+), cytotoxic T cells (CD3+/CD8), B cells (CD19+), NK cells (CD56+), and cytokine-induced killer cells (CD3+/CD56+). Cytokine-induced killer (CIK) cells show surface markers of T cells (CD3+) and NK cells (CD56+). The CIK cell is thought to be of T cell origin, yet CIK cells possess the NK marker yielding the phenotype of CD3+CD56+. T regs and T suppressor cells will also be identified.

9.8.1 Peripheral blood monocytes/macrophages will be mobilized. These cells express various surface receptors, representing various biological functions such as adhesion, phagocytosis (CD11b/CD18, CD11c/CD18, CD16), antigen-presentation (HLA-DR, ICAM-1), differentiation (transferrin receptor, CD71), receptor for LPS (CD14) and initiation of the coagulation cascade (Tissue factor, CD142). To test for the presence of monocytes/macrophages, we will use antibodies directed against CD64/CD16/CD45/CD14.

9.9 Cytotoxicity of the mobilized effector cell population: Standard 4-hour ^{51}C release cytotoxicity assays will be used to determine cytotoxic potential of the mobilized effector cells against NK-sensitive and LAK-sensitive K562 (CML) and NK-resistant, LAK-sensitive Daudi (lymphoma) human tumor cell lines. Three effector to target ratios will be evaluated (10:1, 50:1, 100:1). The percent lysis will be calculated using the standard formula with data presented as mean +/- SEM. Controls will be patient's own lymphocytes prior to stem cell mobilization. The change in cytotoxicity comparing baseline sample and a sample from the apheresis product will be presented. Internal controls consisting of media only will be used.

9.10 CD3+ CD8+ CTL Cytotoxicity; Isolation of the cytotoxic effector cells: This functional assay evaluates CD3 + T cell re-directed lysis of target cells. Briefly, mononuclear cells will be isolated from blood or PBSC and cultured overnight in medium with or without IL-2 (10 U/ml). Cells will be assayed the next day for their ability to lyse chromium-labeled Fc Receptor (FcR)-bearing P815 target cells (Myeloid cells). A 6-hr antigen-independent redirected lysis assay is employed using anti-CD3 MAb (OKT3) for CTL lytic activity and a control (no antibody- to measure background levels of lysis). The use of an isotype control MAb W6/32 (directed against a monomorphic HLA-A, HLA-B, and HLA-C determinant) has demonstrated that this assay is specific. The benefits of this assay over a standard Cr^{51} assay is that the addition of OKT3 "recruits" all CD3+ T cells and is specific to CD3+ T cells. This recruitment allows the Fc receptor of the OKT3 to be directed against the FcR of the target cells (P815 cells). Employing a method we previously developed for T cell subset depletion using antibodies conjugated to magnetic beads (Dynal, Oslo Norway), the immune-mobilized mononuclear cells will be depleted of various T cell subsets and the CD3 Re-Directed Lysis Test repeated. Murine anti-human CD3, CD4, CD8 and CD56 antibodies conjugated to goat anti-mouse magnetic beads (Dynal, Oslo Norway) will be

used. After depletion and prior to performing the cytotoxicity assay, the efficacy of cell subset depletion will be assessed by flow cytometry using FITC-labeled antibodies directed against CD3, CD4, CD8 and CD56 and analyzed using a lymphocyte gate.

9.11 Intracellular cytokine analysis: We will determine if the T cells within the mobilized product are of T helper lymphocyte type 1 (Th1) or T helper lymphocyte type 2 (Th2) origin. $CD4^+$ helper T cells differentiate into two effector T cell populations, called Th1 cells or Th2 cells. Th1 cells promote cell-mediated immunity and secrete IFN-γ, IL-2, IL-10, and TNF-α. These cytokines promote cytotoxic T lymphocyte proliferation and macrophage activation resulting in destruction of tumor cells. Th2 cells are required for humoral immunity and secrete IL-4, IL-5, IL-9, and IL-13. We have previously published our experience using either flow cytometry or ELISA to examine intracellular cytokines (**22**).

10.0 CRITERIA FOR RESPONSE AND TREATMENT ENDPOINTS

10.1 Primary Objective

The primary objective of this clinical trial is to determine if a lower dose of cyclophosphamide combined with filgrastim can mobilize an adequate number of CD34+ progenitor cells with less toxicity.

Details of this objective, as well as the Secondary and Exploratory objectives are listed within the "Objectives".

If the lower dose arm demonstrates non-inferiority at completion of patient accrual, then additional patients will be added to the lower dose arm to confirm non-inferiority or superiority. The number of patients needed to answer this will be based on statistical evaluation of the preliminary results (see Statistical Analysis).

10.2 Secondary Objectives:

10.2.1 Define resource utilization during the mobilization and apheresis processes:

- Transfusions of red blood cells
- Transfusion of platelets
- Hospitalizations
- Incidence of febrile neutropenia

10.3 Exploratory Objectives

10.3.1 Determine the post-transplant engraftment of neutrophils and platelets.

10.3.2 Qualitative and quantitative analyses of mobilized lymphocytes.

10.3.3 Translational studies examining the mobilized stem cell product and characterizing their functional abilities. This will be performed by determining the following:

- Phenotypic analyses of early progenitor cells
- Cytotoxicity of the mobilized effector cells
- CD3+ CD8+ CTL Cytotoxicity; Isolation of the cytotoxic effector cells
- Intracellular cytokine analysis of the mobilized effector cells

11.0 REMOVAL OF PATIENTS FROM PROTOCOL and STOPPING RULES

11.1 Any patient may request removal from the trial at any time. In addition, the treating physician may remove a patient from the trial at any time during treatment. If a patient requests withdrawal, the patient's samples will not be used for analyses.

11.2 Monitoring of toxicities will terminate on the last day of collection, since treatment-related toxicities occur during this time period. Patients who complete mobilization will be considered "off treatment" on the last day of collection. Patients will be considered "off protocol" after engraftment. There will be no specified follow up beyond the off treatment period. However, should any life threatening event directly linked to the study take place within 2 weeks post-mobilization, the investigator shall use his/her discretion is reporting the event to the appropriate committees.

11.3 Mobilization Failures: Any patient who "fails" to mobilize will be removed from the trial. The term "mobilization failure" refers to an inadequate collection of CD34+ cells needed for an autologous stem cell transplant. This definition is based on the absolute number of CD34+ cells collected or the inability to collect a specified number of cells in a certain number of leukapheresis. Mobilization failure can also be predicted by the number of CD34+ cells mobilized into the peripheral blood following the mobilization treatment. If the number of CD34+ cells in the blood is low, the apheresis process will not collect enough cells.

11.4 Based on a review of the literature, 8% to 13% of myeloma patients will not mobilize cells (**1-4**). Using an estimated 10% of patients failing to mobilize in each group, we will need to accrue 44 patients to have 40 eligible patients. Due to the complicated clinical course of these patients and factors known to make collection of autologous cells difficult, including patients' age, previous therapy, previous radiation, the trial will be stopped if 20% of patients (n = 4) receiving the intermediate dose of cyclophosphamide (3 gms/m^2) do not mobilize or 30 % of patients (n = 6) receiving the low dose cyclophosphamide (1.5 gms/m^2) fail to mobilize.

12.0 REPORTING OF SERIOUS ADVERSE EVENTS AND UNANTICIPATED PROBLEMS

12.1 Since this trial represents standard of care treatment, we do not anticipate severe or life threatening toxicities. In fact, many centers use a much higher dose of cyclophosphamide (5 gms/m^2) for mobilization, then commonly used at DHMC. We will closely monitor for any side effects or toxicities.

12.2 Patients will be instructed to report the occurrence of any adverse event. An adverse event is any undesirable event occurring from the time of consent until the last leukapheresis. Adverse events will be graded according to the NCI Common Toxicity Criteria Version 4.0. A copy of the CTC version 4.0 can be downloaded from the CTEP home page (http://ctep.info.nih.gov). All appropriate treatment areas should have access to a copy of the CTC version 4.0. Adverse events and unanticipated problems will be reported to The Dartmouth Committee for the Protection of Human Subjects (CPHS) as per their statement found at http://www.dartmouth.edu/~cphs/docs/aedsmmemo.pdf using their Serious Adverse Event (SAE) Reporting Form or their Reporting Form for An Unanticipated Problem Involving Risks to Subjects or Others (UPR)for Clinical Trials found at http://www.dartmouth.edu/~cphs/tosubmit/forms/.

Adverse events to be reported to the CPHS are: any adverse experience, defined as any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in the research), that is considered:

– Serious: Death; a life-threatening adverse drug experience; inpatient hospitalization or prolongation of existing hospitalization; a persistent or significant disability or incapacity; or a congenital anomaly or birth defect; and

– Unexpected: Any adverse experience, the specificity or severity of which is not consistent with the current investigator brochure or consent form; and

– Possibly related: There is a reasonable possibility that the incident, experience, or outcome may have been associated with the procedures involved in the research; and is experienced by a participant in a trial open at a site subject to review by the CPHS.

The following definitions will be used to assess causality:

No: The clinical adverse event is definitely unrelated to study procedures (e.g., does not follow a reasonable temporal sequence from study procedure, present prior to procedure, etc.)

Unlikely: The study procedures do not have any reasonable association with the observed experience; however, relationship cannot be definitely excluded.

Possibly: The connection with study procedures appears feasible, but cannot be excluded with certainty (e.g., follows a reasonable temporal sequence from procedure, but may also be related to other known factors).

Probably: The clinical experience appears related to the study procedures with a high degree of certainty (e.g., follows a reasonable temporal sequence from procedure and abates upon termination of the procedure, cannot be reasonably explained by known characteristics of the patient's clinical state or other modes of therapy administered to the patient, etc.)

An unanticipated problem involving risks to subjects or others is defined as any incident, experience, or outcome that meets each of the following criteria:

- Unanticipated in terms of nature, severity, or frequency given: (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and consent document; and (b) the characteristics of the subject population being studied; and
- Possibly related to participation in the research means there is a reasonable possibility that the incident, experience, or outcome may have been associated with research participation; and
- The problem suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, emotional, economic, legal, or social harms) than was previously known or recognized.
- Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

We will monitor and record unexpected toxicities related to the treatment and all $\geq$ Grade 4 toxicities.

13.0 STATISTICAL CONSIDERATIONS

13.1 Doses of cyclophosphamide commonly used for mobilization will be examined with a standard a dose of filgrastim. The primary objective of this clinical trial is to determine if a lower dose of cyclophosphamide combined with filgrastim can mobilize an adequate number of CD34+ progenitor cells with less toxicity. We postulate that the low dose cyclophosphamide (1.5 gms/m^2) mobilization regimen will be as efficacious as the intermediate dose (3 gms/m^2). In the event that a patient is not evaluable, that patient will be replaced by enrolling another patient. Toxicity will be tabulated according to type and grade, both overall and according to dose group. Toxicity will be evaluated during mobilization and collection.

13.2 The trial is designed as a non-inferiority trial, meaning we will be examining if the lower dose of cyclophosphamide will mobilize a similar number of cells with fewer toxicities, when compared with a higher dose of cyclophosphamide. Based on this assessment, 40 patients will be treated. With 20 patients in each arm, we can achieve 80% power to detect non-inferiority using a one-sided, two-sample t-test. If the difference between the average number of apheresis required to collect cells for lower dose arm and higher dose arm is no greater than 0.5. The true difference between the means is assumed to be 0. The significance level (alpha) of the test is 0.025 and standard deviations are 0.55 for both arms.

13.3 Based on a review of the literature, 8% to 13% of myeloma patients will not mobilize cells (**3**). Using an estimated 10% of patients failing to mobilize in each group, we will need to accrue 44 patients to have 40 eligible patients. Due to the complicated clinical course of these patients and factors known to make collection of autologous cells difficult, including patients' age, previous therapy, previous radiation, the trial will be stopped if 20% of patients (n = 4) receiving the intermediate dose of cyclophosphamide (3 gms/m^2) do not mobilize or 30 % of patients (n = 6) receiving the low dose cyclophosphamide (1.5 gms/m^2) fail to mobilize.

13.4 For other clinical outcomes, such as number of apheresis required to collect an adequate number of cells and the number of cells collected, we will use two sample t-test to evaluate if there is any statistical significance between the two arms. Where necessary, we will use transformations (e.g., logarithm and square root) to adjust for skewed distributions. We will use 2-dimensional scatterplots to visualize the associations and to ensure the assumptions of t-test are not violated. All statistical tests will be one-sided, and the overall type I error will be 0.025. Engraftment rates will be estimated for the overall sample as well as for each dose group. Confidence intervals will be constructed using exact binomial methods. Laboratory analysis of the parameters related to mobilized cells will include overall summaries and graphical displays. We will attempt to fit linear and non-linear models as appropriate based on the data summaries.

13.5 We do not anticipate any long-term toxicities. As a result, after collection of the cells, patient follow-up will be stopped except for collection of engraftment data, if available.

13.6 SUMMARY of PRELIMINARY RESULTS: We have analyzed the preliminary data and some of the results are presented below. In particular, the specific aim of the

trial was to show that the number of CD34+ cells and the number of mononuclear cells collected were similar in each arm (Table 3).

Table 3 Summary of Progenitor Cell Collection

Variables	***COHORT 1*** **Cyclophosphamide 1500 mg/m^2 n = 19 patients**	***COHORT 2*** **Cyclophosphamide 3000 mg/m^2 n = 20 patients**	**P value**
Total # of MNC (10^{10})	**5.2 (2.9 – 20.7)**	**3.8 (1.9 – 7.1)**	**0.03**
Total # of CD34+ cells (10^8)	**7.2 (2.2-49.9)**	**10.5 (1.9 – 29.4)**	**0.6**

MNC = mononuclear cells

The results indicate that patients receiving the lower dose of cyclophosphamide collected more total mononuclear cells when compared with the higher dose of cyclophosphamide (p = 0.03). The number of CD34+ cells collected is lower in the lower dose arm (7.2 x 10^8) compared with the higher dose arm (10.5 x 10^8), although this is not statistically significant (p = 0.6). Although the lower number of CD34+ cells collected in the lower dose arm is not statistically significant, this is still a critical finding since the difference between the two arms might be *clinically* significant.

Since the number of CD34+ cells is a more important clinical parameter used to determine optimal cell collection and to determine the optimal number of cells to infuse, more patients should be accrued to the lower dose arm to verify the number of CD34 + cells that are collected does not decrease. Based on preliminary analyses of 19 patients who were treated in the lower dose arm, approximately 13 more patients would need to be accrued to the lower dose to confirm that the number of CD34+ cells collected remains within the current range and does not decrease. The results from these additional 13 patients will be combined with the results from the other participants previously treated on the lower dose arm and compared as a group with the high dose arm. The addition of 13 patients (32 patients total in the lower dose arm) would achieve 80% power to confirm a difference in the number of CD34+ cells collected between the two cohorts, with a *p* value (alpha) of 0.05, using a two-sided two-sample t-test. We recognize that this new addition may interfere with the previous randomization. We will use T test and Chi-square to determine if there is any significant difference between the two arms on all potential confounders. If one or more variables are identified, we will use linear regression model to include them as confounders.

14.0 STUDY MONITORING, AUDITING AND INSPECTION

14.1 Safety and Data Monitoring

This study will be monitored by the Data Safety Monitoring and Accrual Committee (DSMAC) of the Norris Cotton Cancer Center. The Committee meets quarterly to review accrual rates and information of all studies that have accrued participants. The Clinical Cancer Review Committee (CCRC) determines the frequency of DSMAC review. The DSMAC has the authority to suspend or to recommend termination to the CCRC of all research activities that fall within its jurisdiction. In the event that a study is suspended or terminated by the DSMAC, that information will be forwarded to the CPHS (Dartmouth IRB) office.

The DSMAC will monitor this trial. In particular, areas that will be monitored include accrual to the trial, toxicity associated with the treatment and patient outcomes (the "Objectives"). Since this trial represents standard of care treatment, we do not anticipate severe or life threatening toxicities. In fact, many centers use a much higher dose of cyclophosphamide (5 gms/m^2) for mobilization, then commonly used at DHMC. We will closely monitor for any side effects or toxicities. Stopping rules will be followed, as outlined in Section 11. Briefly, the trial will be stopped if 20% of patients (n = 4) receiving the intermediate dose of cyclophosphamide (3 gms/m^2) do not mobilize or 30 % of patients (n = 6) receiving the low dose cyclophosphamide (1.5 gms/m^2) fail to mobilize.

14.2 On-site monitoring

Clinical research monitoring for regulatory compliance and data integrity will be conducted according to the NCI-approved NCCC Data and Safety Monitoring Plan. Internal monitoring is conducted by appropriately trained staff of the NCCC Office of Clinical Research and Dartmouth-Hitchcock Medical Center Clinical Trials Office who are not involved in the study. This monitoring will include periodic assessment of the regulatory compliance, data quality, pharmacy records and study integrity. Study records will be reviewed and directly compared to source documents and the conduct of the study will be discussed with the investigator. Monitors may request access to all regulatory documents, source documents, CRFs, and other study documentation for on-site inspection. Direct access to these documents is guaranteed by the investigator, who must provide support at all times for these activities.

14.3 Auditing and Inspection

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable Dartmouth research compliance and quality assurance offices. The investigator will permit study protocol related audits and inspections by the Dartmouth CPHS, government regulatory bodies, and the Dartmouth compliance and quality assurance groups of 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.).

14.4 Record Retention

Following closure of the study, the investigator will maintain all site study records in a safe and secure location. The records are maintained to allow easy and timely retrieval when needed (e.g., audit or inspection) and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting

systems, and staff. Upon completion of study analysis, research information is stored in Dartmouth College Records Management off-site storage located at 6218 Etna Road, Hanover, NH 03755. Documents are shredded on site after 50 years of storage.

Electronic case report forms, participant, and study information will be kept in the Velos eResearch password-protected database (or equivalent) indefinitely.

15.0 HUMAN SUBJECTS

15.1 This is a randomized study. To enter eligible patients or discuss a patient's eligibility, please contact Dr. Kenneth R. Meehan or the Clinical Research Associate (Bridget Labrie at 603-650-6227). No patients shall be entered on study without consultation with the Principal Investigator or CRA.

15.2 Patient care and status will be monitored by a Transplant/Hematology Physician and a designated Data Manager. All data will be maintained on a closed database with each subject identified by a unique patient number (UPN) with access to patient names only for those involved in clinical care. All patients will provide informed consent prior to study entry. Necessary information will be forwarded to the Center for International Blood and Marrow Transplant Registry (CIBMTR). Each patient will be fully informed concerning this study, including pertinent adverse reactions. All institutional or other Federal regulations and guidelines concerning informed consent will be fulfilled.

15.3 Gender and Minority Inclusion for Research Involving Human Subjects: The clinical trial is open to all patients with the hematologic malignancies as outlined within the "Eligibility Criteria" of the trial. All races and both genders are eligible. Given the geographic location of Dartmouth-Hitchcock Medical Center and the Norris Cotton Cancer Center, we anticipate the majority of patients will be Caucasian with an equal distribution of males and females.

15.4 Participation of Children: Stem cell transplants in pediatric patients are not performed at Dartmouth.

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Appendix A

Dartmouth-Hitchcock

Job Aid	Stem Cell Mobilization Job Aid - Blood and Marrow Transplant	ID:	9624
Keywords	Not Set		
Department	Blood and Marrow Transplant Program		

I. Purpose

The purpose of this Job Aid is information on Hematopoietic Progenitor Cells, Apheresis (HPC-A) mobilization for healthy allogeneic donors and patients undergoing autologous stem cell transplantation.

Patients enrolled in a clinical trial, refer to the specific trial protocol, as it may utilize Sargramostim or Pegfilgrastim for mobilization and it may stipulate alternative specifications for colony stimulating factor (CSF) dose schedule.

A. CSF Medication List:

1. Filgrastim (granulocyte colony stimulating factor, G-CSF, Neupogen®)
   *the primary colony stimulating factor utilized at D-H for PBSC mobilization
2. Sargramostim (granulocyte-macrophage colony stimulating factor, GM-CSF, Leukine®)
3. PEG-filgrastim (Neulasta®)
4. Plerixafor (Mozobil)

B. Pre-Mobilization

a. All candidates for peripheral blood stem cell (PBSC) collection have peripheral venous access of the upper extremities assessed in the Apheresis area prior to initiation of the stem cell mobilization regimen.
   a. Once the donor has been assessed:
      1) Apheresis nurse notifies the Blood and Marrow Transplant Nurse Coordinator if placement of a central venous access device is required.
   b. Donors with inadequate venous access require placement of a temporary or a 3-lumen pheresis catheter.

C. Mobilization

1. Standard G-CSF Mobilization

    a. Growth factor is initiated by Provider five days prior to the onset of stem cell collection.

    b. Subcutaneous G-CSF is used to mobilize peripheral blood stem cells.

2. Routinely, collection begins on the fifth day if the peripheral blood CD34+ count is greater than 5-10 cells/mcL.

3. Collection continues until the requested CD34+/kg recipient number has been reached, generally greater than 2-3 x 10e6 cells/kg recipient.

4. Patients that fail to mobilize, consideration is given for further attempt at PBSC collection or to proceed with a bone marrow harvest.

D. CSF Medication List

1. **Filgrastim** -Granulocyte colony stimulating factor, G-CSF, Neupogen®
   *The primary colony stimulating factor utilized at D-H for PBSC mobilization

    a. Filgrastim is generally considered to be the CSF of choice for PBSC mobilization.

    b. Filgrastim may be administered as a single agent to allogeneic donors; as a single agent or following chemotherapy for autologous stem cell collection.

    c. Filgrastim may be administered as a single agent to allogeneic donors; as a single agent or following chemotherapy for autologous stem cell collection.

    d. If post chemotherapy, begin at least 24 hours after the last dose of chemotherapy.

    e. Administration continues until optimal stem cell collection is completed.

2. **Sargramostim** -Granulocyte-macrophage colony stimulating factor, GM-CSF, Leukine®

3. **PEG-filgrastim** (Neulasta®)

4. **Plerixafor (Mozobil**

5. **Cyclophosphamide (Cytoxan)** GCSF Mobilization

   a. Cyclophosphamide is given in conjunction with IV fluid hydration

   b. Mesna is given with Provider order 15 minutes prior to Cyclophosphamide then at dose four and 8 hours following Cyclophosphamide with provider order..

   c. Filgrastim is given on day 3 of mobilization with provider order

   d. CBC/differential checks on days 4, 6, 8 locally, then on day 11-12 at D-H with associated peripheral blood CD34 cell count with provider order.

   e. Routinely, collection of cells will begin on day 11 or 12 and the peripheral blood CD34+ count is greater than 5-10 cells/ mcL.

   f. Collection of cells continues until the requested CD34+/kg recipient number has been reached, generally greater than 2-5x10e6 cells/kg recipient depending on disease.

   g. For patients that fail to mobilize, consideration is given for further attempt at HPC-A collection with provider order of G-CSF & Plerixiflor (Mozobil) or patient proceeds with a bone marrow harvest.

6. Chemotherapy / G-CSF Mobilization

   a. The majority of the lymphoma patients have been treated with different chemotherapy regimens ie. RICE, ESHAP, EPOOCH, and IVAC.
   b. The BMT program utilizes those cycles of chemotherapy and has added G-CSF to the regimen starting 24hours after last dose of chemotherapy is given.
      1) Filgrastim is recommended as first line with provider order.
      2) CBC/diff laboratory checks 2-3x week locally, then on day 12-14 at D-H with associated peripheral blood CD34 cell count with provider order.
      3) Routinely, collection of cells begins between day 12-14 with the peripheral blood CD34+ count is greater than 3-10 cells/mcL.
      4) Collection continues until the requested CD34+/kg recipient number has been reached generally greater than 2-5 x 10e6 cells/kg recipient depending on disease.

7. Adverse Effect Management

    a. CSFs are generally well-tolerated.
    b. Constitutional symptoms are common.
    c. The majority of patients receiving CSFs experience:
        1) Bone pain
        2) Fevers have also been associated with CSF use, particularly with sargramostim.

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Appendix B

Dartmouth-Hitchcock

Job Aid	Pre-Transplant Allogeneic and Autologous Recipient Evaluation and Selection Job Aid - Blood and Marrow Transplant	ID:	10052
Keywords	Not Set		
Department	Hematology/Oncology		

I. Purpose

The purpose of this procedure is to formalize guidelines pertaining to patient suitability and eligibility for allogeneic and autologous hematopoietic stem cell transplantation and to standardize the process of evaluating and selecting prospective hematopoietic stem cell recipients (peripheral blood *and* bone marrow) to achieve optimal assessment and minimization of potential risks during transplant.

The recipient of conditioning therapy followed by allogeneic or autologous bone marrow or peripheral blood stem cell infusion must be evaluated for all potential risks from this procedure, including the stem cell mobilization and collection process (autologous recipient), chemotherapy regimen (high-dose or reduced intensity or non-myeloablative), stem cell infusion, infectious complications, organ compromise, and graft-versus-host disease (allogeneic recipient). These issues require early thoughtful discussion with the prospective hematopoietic recipient and referring physician, along with consideration of relative risk in the context of the specific medical history and overall state of health of this individual.

Established requirements for high-dose chemotherapy followed by allogeneic or autologous stem cell transplantation are outlined below, *subject to interpretation and potential modification*, depending on the overall status of the patient in question and circumstances surrounding the transplant.

The patient eligibility is discussed in the weekly transplant clinical meetings and a consensus decision is made to proceed or not by the BMT team.

a) General considerations for eligibility

- Recipient has chemotherapy-sensitive disease & attainment of minimal residual disease and no second active malignancy. Disease status will be evaluated using accepted means based on the patient's diagnosis

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- Potential Malignancy
  - Female – pap smear, mammogram
  - Male – prostate exam and/or PSA
  - Colonoscopy – pending age and risk factors.

- Adequate organ function.
  - Echo/Muga – cardiac ejection fraction greater than or equal to 45%.
  - EKG – no evidence of potentially life-threatening cardiac dysrhythmia.
  - Pulmonary function tests – FVC / FEV1 greater than or equal to 50%, and DLCO greater than or equal to 50% predicted.
  - Chest x-ray – R/O lung infection or process that would indicate recipient @ high risk of developing lung issues/complications.
  - 24 hr urine clearance or Glomerular Filtration Rate (GFR) greater than 50 ml/min.
  - Liver function: total bilirubin less than or equal to 2.0 and transaminases.
  - No pregnancy

- No life-threatening viral exposures.
  - Hepatitis B Core Antibody
  - Hepatitis B Surface Antigen
  - Hepatitis C Virus
  - HIV 1/2 Antibody
  - HTLV I/II Antibody
  - Nat Multiplex
  - Syphillis Serology
  - West Nile Virus NAT
  - Chagas Antibody
  - CMV Antibody
  - Herpes simplex virus IgG
  - Toxoplasmosis antibody
  - Varicella zoster virus IgG
  - EBV (Epstein Bar Virus) nuclear IgG

- No life-threatening co-morbidities that would likely compromise the patient's clinical care and chance for optimal post-transplant survival.

- Eradication of any active pre-transplant infection. A dental assessment must be done prior to transplant.

- Age, auto/reduced intensity conditioning and non-myeloablative less than or equal to 75 years and myeloablative conditioning less than or equal to 60 years.

- Karnofsky performance score greater than or equal to 70%

- Psychosocial assessment addressing barriers to transplant (financial, lack of caregivers, and compliance issues). If a barrier is identified, team will discuss and determine if patient can proceed to transplant.

- Allogeneic transplant patients must have an available HLA-matched related or unrelated donor. (10/10 match; 9/10 match feasible, depending on locus of mismatch)

- Pre-transplant stem cell goal of 2-3x10^6 CD34 positive cells per kilogram recipient weight.

- Patients registered on specific protocols will clearly meet the requirements of that protocol.

b) Other points to consider:

- Venous access assessment
    - All patients will have a 3 lumen tunneled CVC line placed at time of transplant.

- Radiation Oncology Consultation
    - When total body irradiation (TBI) is intended as part of the pre-transplant conditioning regimen, a formal request for Radiation Oncology consultation will be initiated by the BMT nurse coordinator.

- Biological product deviations (case-specific basis)
    - A transplant physician will document in the recipient's medical record the prospective donor's suitability for stem cell donation prior to initiation of the recipient's conditioning therapy. In the event of circumstances where a deviation from the standard donor criteria for transplant is noted, including biological product deviations, appropriate rationale for donor selection will be required in writing, along with the informed consent of both the donor and the recipient. If indicated, this will also reflect consensus from a weekly BMT Team Meeting discussion, documented in writing. In the event of a biological product deviation (stem cell contamination, damage during storage, or suboptimal stem cell yield), written documentation of discussion with and approval for use (including the rationale) by the Director of the Dartmouth Hitchcock Transfusion Medicine Service will be required.

- On a case by case basis, patients will be considered for their appropriateness for outpatient stem cell transplant (autologous or non-myeloablative allogeneic), depending on several factors, including but not necessarily limited to the following:
    - Personal patient and caregiver desire for and commitment to outpatient transplant

- Patient compliance and caregiver competency/reliability
- Appropriate home and/or local environment availability (e.g., hotel, VNA services)
- Suitability of conditioning regimen for outpatient therapy
- No other medical condition that may complicate outpatient therapy.

- Re-evaluation of transplant assessment will occur in these two instances:
  - If more than 12 weeks has elapsed between harvest or peripheral blood stem cell (PBSC) collection and transplant, the need for reconfirmation of eligibility will be assessed.
  - Patients who do not meet the transplant criteria upon their initial assessment will be re- evaluated when deemed appropriate by the transplant physician. The patient's treatment plan will take into consideration the individual issue(s) which have precluded the patient from transplant, determinations of whether they are modifiable, and the appropriate time frames for re-evaluation.

FOR ALLOGENEIC TRANSPLANT PATIENTS ONLY

- As allogeneic patients are evaluated, the EBMTR and Hematopoietic Stem Cell Transplant Co-morbidity Index (HCT-CI) scores will be assessed in an effort to select those patients that will optionally do best with an allogeneic stem cell transplant. These results will be documented in the patient's medical record.

EBMT Risk Score

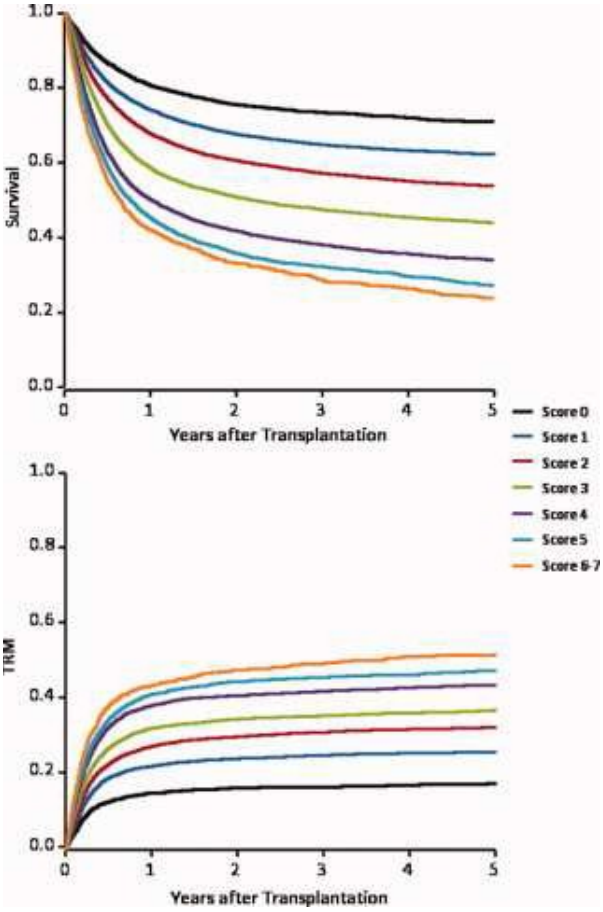
- It is sometimes difficult to determine a patient's risk when deciding if a patient is a candidate for transplant. The European Blood and Marrow transplant (EBMT) Group developed a risk score to assess potential allogeneic recipients before transplant. The EBMTR group identified 5 patient and donor characteristic, including:
  - Patient age
  - Disease stage
  - Time from diagnosis to transplant,
  - Donor type
  - Donor-recipient gender
- These 5 traits were examined in 56,505 allogeneic transplant patients (myeloablative and non-ablative regimens), with various hematologic malignancies and were predicative of survival and treatment- related mortality.

Table 1. European Group for Blood and Marrow Transplantation Risk Score Definition

Risk Factor	Score Point
Age of the patient, y	
Less than 20	0
20-40	1
Greater than 40	2
Disease stage	
Early	0
Intermediate	1
Late	2
Time interval from diagnosis to transplant, months*	
Less than 12	0
Greater than 12	1
Donor type	
HLA-identical sibling donor	0
Unrelated donor	1
Donor-recipient sex combination	
All other	0
Donor female, male recipient	1

*Does not apply for patients transplanted in first complete remission (score 0).

Figure 1: Risk score for outcome after allogeneic hematopoietic stem cell transplantation



Survival (Top) and transplant-related mortality (TRM) (Bottom) of 56,605 patients with an allogeneic hematopoietic stem cell transplantation (HSCT) for an acquired hematological disorder is shown by risk score. Graphs reflect probability of survival (Top) and transplant-related mortality (Bottom) over the first 5 years after HSCT.

HCT-CI

- The Hematopoietic Stem Cell Transplant Co-morbidity Index was developed by Sorror, et. al. and addresses a patient's survival and non-relapsed mortality based on specific patient characteristics.

Table 2. Definitions of comorbidities included in the HCT-CI

Comorbidity	Definitions of comorbidities included in the HCT-CI	HCT-CI weighted scores
Arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias	1
Cardiac	Coronary artery disease*, congestive heart failure, myocardial infarction, or EF less than or equal to 50%	1
Inflammatory bowel disease	Crohns disease or ulcerative colitis	1
Diabetes	Requiring treatment with insulin or oral hypoglycemics but not diet alone	1
Cerebrovascular disease	Transient ischemic attack or cerebrovascular accident	1
Psychiatric disturbance	Depression or anxiety requiring psychiatric consult or treatment	1
Hepatic, mild	Chronic hepatitis, bilirubin greater than ULN to 1.5 x ULN, or AST/ALT greater than ULN to 2.5 x ULN	1
Obesity	Patients with a body mass index greater than 35 kg/m^2	1
Infection	Requiring continuation of antimicrobial treatment after day 0	1
Rheumatologic	SLE, RA, polymyositis, mixed CTD, or polymyalgia rheumatica	2
Peptic ulcer	Requiring treatment	2
Moderate/severe renal	Serum creatinine greater than 2 mg/dL, on dialysis, or prior renal transplantation	2
Moderate pulmonary	DLco and/or FEV_1 66%-80% or dyspnea on slight activity	2
Prior solid tumor	Treated at any time point in the patient's past history, excluding nonmelanoma skin cancer	3
Heart valve disease	Except mitral valve prolapse	3
Severe pulmonary	DLco and/or FEV_1 less than or equal to 65% or dyspnea at rest or requiring oxygen	3
Moderate/severe hepatic	Liver cirrhosis, bilirubin greater than 1.5 x ULN, or AST/ALT greater than 2.5 x ULN	3

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

Table 3: HCT-CI scores, 2 year survival and hazard ratios for NRM (Non-Relapse Mortality)

HCT-CI					
		NRM		Survival	
Score	N	HR*(95% CI)	2-year, %	HR*(95% CI)	2-year, %
0	38	1.0	14	1.0	71
1 to 2	34	1.42 (0.8-2.7)	21	1.31 (0.8-2.0)	60
3 or more	28	3.54 (2.0-6.3)	41	2.69 (1.8-4.1)	34

* Adjusted for age, disease risk, and conditioning.

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Related Job Aids:	Pre-Transplant Patient-Recipient Evaluation Allogeneic Stem Cell Transplant Job Aid - Blood and Marrow Transplant Pre-Transplant Donor/Patient Autologous Evaluation Job Aid - Blood and Marrow Transplant		

Job Aid	Selection of Preparative High-Dose Chemotherapy Regimens Job Aid- Blood and Marrow Transplant	ID:	8412
Keywords	Not Set		
Department	Blood and Marrow Transplant Program		

I. Purpose

The purpose of this Job Aid is educational information surrounding the selecting of conditioning therapy prior to hematopoietic stem cell transplantation (HSCT).

A. Selection of Appropriate Patients for Hematopoietic Stem Cell Transplant

- The recipient of conditioning therapy followed by allogeneic or autologous bone marrow or peripheral blood stem cell infusion must be evaluated for all potential risks from this procedure, including the stem cell mobilization and collection process (autologous recipient), high-dose chemotherapy, stem cell infusion, infectious complications, organ compromise, and graft-versus- host disease (allogeneic recipient).

- These issues require early thoughtful discussion with the prospective hematopoietic recipient, along with consideration of relative risk in the context of the specific medical history and overall state of health of this individual.

- Established eligibility for high-dose chemotherapy followed by allogeneic or autologous stem cell transplantation and is *subject to interpretation and potential modification,* depending on the overall status of the patient in question and circumstances surrounding the transplant.

B. Selection of High-Dose Chemotherapy Regimens Prior to Hematopoietic Transplant

- The conditioning (preparative) regimen is a critical factor in the hematopoietic stem cell process, with objectives that differ between the allogeneic and autologous settings:

- Conditioning Regimen Objectives

a. Allogeneic
   - Ablation of host immunity (to prevent rejection of the transplanted donor graft)
   - Tumoricidal activity (when malignant disease is present)

b. Autologous
   - Tumoricidal activity
   - Steep dose-response curve
   - Lack of cross resistance with other drugs
   - Low extra-medullary dose-limiting toxicity

- More specific factors in the selection of the pre-transplant preparative agents relate to potential toxicities of a potential conditioning regimen in the context of the patient's pre-transplant status, the relative toxicity of prior therapies and existing comorbidities. For example, a patient with a history of Hodgkin's disease including a prior mediastinal mass that required radiation would not be an optimal candidate for a BCNU-containing conditioning regimen, given the combined risks for interstitial pneumonitis.

- Alternately, older patients with a characteristically lower threshold for neurologic toxicity are less optimal candidates for high-dose cytarabine, given that cerebellar toxicity is a primary extra- medullary side effect of this agent.

- The extra-medullary dose limiting toxicities of several common conditioning agents are listed below:

Extra-medullary Dose Limiting Toxicities	
Therapy	**Possible Toxicities**
Carmustine (BCNU)	lung (interstitial pneumonitis)
Etoposide (VP-16)	mucositis; liver
Cytarabine (Ara-C)	CNS ataxia; mucositis
Busulfan	veno-occlusive disease (VOD); seizures; lung; mucositis
Cyclophosphamide	hemorrhagic cystitis; heart failure
Total body irradiation (TBI)	lung; heart

- Commonly Used Conditioning Regimens for HSCT

  a. Autologous

     - Melphalan
     - Melphalan & Velcade
     - CBV – Cyclophosphamide, Carmustine & Etoposide

- BEAM – Carmustine, Etoposide, Cytarabine & Melphalan

b. Allogeneic

- Non-Myeloablative
  - Fludarabine/Total Body Irradation (Flu/TBI)
  - Fludarabine/Busulfan (Dosing for Busulfan 9.6 mg/kg)
- Reduced Intensity
  - Fludarabine/Cyclophosphamide (Dosing for Cytoxan 120 mg/kg)
  - Fludarabine/Melphalan
  - Flurabine/Bulsulfan (Dosing for Busulfan 6.4 mg/kg)
- Myeloablative
  - Bulsulfan/Cyclophosphamide (BuCy)
    - Cyclophosphamide/Total Body Irradiation (Cy/TBI)
    - Fludarabine/Cyclophosphamide (Dosing for Cytoxan 3 mg/m^2)

- Ultimately, the final decision regarding the choice of pre-transplant conditioning regimens is made on the basis of a combination of factors, including patient-related issues (as discussed above), the disease in question (e.g., CBV being used typically for the transplant of patients with lymphoma), and personal experience and preference on the part of the transplant center and its BMT team.

- Each potential transplant patient is discussed 2-3 times at the BMT team meetings (Tuesday or Thursday), with representation from Transfusion Medicine, Cellular Therapy, and Pharmacy. The patient's medical history is reviewed, and selection of a treatment regimen is finalized.

- As a double-check, the BMT Coordinators will confirm the preparative regimen with the Attending when the orders are being written.

References

Gyurkocza B, Sandmaier B. Conditioning regimens for hematopoietic cell transplantation: one

size does not fit all. Blood Jan 2014, DOI: 10.1182/blood-2014-02-514778

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