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A PHASE III STUDY OF FLUDARABINE AND BUSULFAN VERSUS FLUDARABINE, BUSULFAN AND LOW DOSE TOTAL BODY IRRADIATION IN PATIENTS RECEIVING AN ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANT

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BLOOD AND MARROW TRANSPLANTION PROGRAM

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ABBREVIATIONS LIST

Abbreviation	Definition
°C	degrees Celsius
µM	Micromolar
20S	20S proteasome subunit
AE	adverse event
ANC	absolute neutrophil count
Bc1-2	B-cell lymphoma-2; a gene that inhibits apoptosis
BSA	body surface area
Bu	busulfan
CAM	cell adhesion molecules
cm	Centimeter
CR	Complete Response
CTCAE	(NCI) Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
dL	Deciliter
DLT	Dose Limiting Toxicity
DNA	deoxyribonucleic acid
FDA	Food and Drug Administration
Flu	fludarabine
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
ht	Height
IκB	I kappa B kinase; cytokine response kinase that activates transcription factor NF-kappa b at serine 32 and 36
ICAM-1	intercellular adhesion molecule 1
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous
IκBα	I kappa B alpha-associated protein kinase
kg	Kilogram
Ki	inhibitory constant
lbs	Pounds

Abbreviation	Definition
m^2	square meters
mg	Milligram
min	Minute
mL	Milliliter
mm^3	cubic millimeters
mmol	Millimole
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NF-κB	nuclear factor-κB
ng	Nanogram
nM	Nanomole
p21	p21(ras) farnesyl-protein transferase
p27	cyclin-dependent kinase inhibitor
p53	tumor suppressor protein with molecular weight of 53 kDa
SAE	serious adverse event
TBI	total body irradiation
US	United States
USP	United States Pharmacopeia
VCAM-1	vascular cell adhesion molecule 1
w/w	weight-to-weight ratio
wt	Weight

1 INTRODUCTION AND STUDY RATIONALE

1.1 Allogeneic transplantation for the treatment of myelodysplastic syndrome, chronic myelogenous leukemia and other myeloproliferative disorders, and acute myeloid leukemia:

The myelodysplastic syndromes are a heterogeneous group of clonal hematologic disorders characterized by bone marrow failure and proliferation of myeloblastic leukemia cells. Patients with MDS develop cytopenias as a result of ineffective hematopoiesis. These cytopenias are believed to be a result of an increase in apoptosis resulting in an increase in futile cell cycling. In addition, the apparently mature and differentiated hematopoietic cells in patients with MDS are functionally impaired. Granulocytes have decreased myeloperoxidase activity (1,2) and platelets have impaired function. Therapy for MDS includes supportive care geared mostly to tranfusional support. Allogeneic transplantation has been shown to offer the possibility of long-term remission and remains the only curative option for patients with MDS. The development of reduced intensity conditioning

regimens expanded the scope of allogeneic transplantation for older patients with MDS. A very large retrospective analysis by the European Blood and Marrow Transplantation Group (3) compared the outcome of 836 patients with MDS treated with either a reduced-intensity conditioning regimen or a conventional regimen before allogeneic transplantation. The 3-year probabilities of progression-free and overall survival were similar in both groups, with a 3-year relapse rate being significantly higher in the reduced-conditioning group, offset by a significantly reduced probability of non-relapse mortality. This demonstrates the importance of the preparative regimen in preventing relapse in this setting.

Acute myeloid leukemia accounts for over 9,000 deaths yearly in the United States. The WHO classification of AML incorporates and interrelated morphology, cytogenetics, molecular genetics and immunologic markers in an attempt to construct a classification that is clinically and prognostically valid. Under this classification the requisite blast percentage in the marrow is $\geq$ 20%. Hematopoietic stem cell transplantation is an established therapeutic modality in patients with AML. An alloreactive immunotherapeutic effect of donor cells has been demonstrated.

No other established therapy applied during complete remission offers as strong an anti-leukemic effect. Transplant-related morbidity and mortality, however, remain obstacles in the successful application of this treatment. More recently, reduced-intensity conditioning has been applied as a therapy for AML. Reduced-intensity conditioning, which includes potent immunosuppressive agents in addition to anti-leukemic agents, effectively permits engraftment of donor hematopoietic stem cells. Several studies have demonstrated that the morbidity and mortality are less with these regimens compared to myeloablative conditioning (4) (5). While the reduced intensity of the conditioning regimen has resulted in reduced non-relapse mortality in patients with AML, some studies have suggested a concomitant increase in relapse as a consequence of lowering the intensity of the cytotoxic agents(6). New conditioning regimens that increase the anti-leukemic effect while maintaining a low regimen toxicity profile, are therefore needed.

Chronic myeloid leukemia (CML) was the first neoplastic disease associated with a chromosomal aberration. The Philadelphia chromosome is a reciprocal t(9;22)(q34;q11) translocation that results in the production of the Bcr-Abl1 fusion protein (previously termed Bcr-Abl), a constitutively active tyrosine kinase. Elucidation of the molecular pathogenesis of CML led to the development of the tyrosine kinase inhibitor (TKI) STI-571, now known as imatinib mesylate. The Food and Drug Administration first approved imatinib in May 2001 for the treatment of patients with chronic-phase (CP) CML after failure of interferon alfa therapy and for the treatment of advanced CML. In December 2002, after positive results from the International Randomized Study of Interferon vs STI571 (IRIS), imatinib was approved for the treatment of patients with newly diagnosed CP-CML. Use of imatinib as first-line therapy has resulted in complete cytogenetic responses (CCyRs) in 65% to 85% of patients with CML. Despite the successes of imatinib in treating CML, some patients' responses to treatment are inadequate. In the IRIS trial, approximately 30% of patients with newly diagnosed CP-CML who were randomized to receive imatinib did not achieve a CCyR within 1 year of treatment. In addition, approximately 10% of patients experienced relapse during 5 years of follow-up, including

approximately 10% who had achieved a CCyR. Higher rates of treatment failure occur in patients with accelerated- or blast-phase disease.

Allogeneic SCT is the only potentially curative treatment for CML. However, since the development of modern TKIs, allogeneic SCT is more commonly performed after patients have received imatinib and second-generation agents and is an important treatment option after treatment failure. Prior imatinib treatment does not adversely affect overall survival, progression-free survival, or nonrelapse mortality after allogeneic SCT, and second-generation TKIs do not appear to increase transplant-related toxic effects. Also, allogeneic SCT is probably the best available therapy for eligible patients with a T315I mutation.

1.2 Fludarabine and busulfan in conditioning regimens:

The combination of fludarabine and intravenous busulfan (FluBu) has become the most commonly used conditioning regimen for allogeneic transplantation. Its safety profile has compared favorably to the previous regimens of cyclophosphamide and TBI or cyclophosphamide and busulfan (BuCy). Andersson et al. reported on 148 patients receiving fludarabine and busulfan for conditioning regimen compared to 67 patients receiving BuCy (7). The groups had comparable pretreatment characteristics, except that FluBu patients were older (46 versus 39 years, P<0.01), more often had unrelated donors (47.3% versus 20.9%, P<0.003), and had shorter median follow-up (39.7 versus 74.6 months). To account for improved supportive care and other unidentified factors that might have affected outcome ("period" effects), 78 acute myelogenous leukemia (AML) patients receiving Melphalan-Flu (MF), treated in parallel during this time (1997-2004) were used to estimate the period effect. The MF patients' outcomes worsened during this period. Therefore, the period effect was unlikely to have explained the greatly improved outcome with FluBu. Patients transplanted with FluBu in their first complete remission (CR1) had a 3-year overall survival and event-free survival (EFS) of 78% and 74% respectively, whereas CR1 patients younger than age 41 had a 3-year EFS of 83%. These results supported replacing BuCy with FluBu. Bredeson et al. compared BuCy to FluBu by performing a retrospective matched-pair analysis comparing outcomes of adult patients treated with either regimen (8). One hundred and twenty cases (FluBu) and 215 matched controls (BuCy) were available for comparison. All FluBu patients also received antithymocyte globulin (ATG). Patients receiving FluBu had significantly less treatment related mortality (12% versus 34%) and grades II-IV acute graft-versus-host disease (15% versus 34%, P<0.001) compared to BuCy patients. The risk of relapse however, was higher in the FluBu patients (42% versus 20%, P<0.001). The risk of chronic GVHD and disease-free survival was similar in the cases and controls. In conclusion, the FluBu regimen has improved the treatment-related mortality but post-transplant relapse remains the main obstacle in the successful treatment of these patients.

The fludarabine, busulfan, TBI (FluBuTBI) regimen has been established in an effort to reduce the relapse rate (9). Russell et al. evaluated a myeloablative regimen of daily busulfan, fludarabine, and 400 cGy total-body irradiation given before allogeneic transplantation. Sixty-four adults with acute leukemia in first and second remission were evaluated. All patients also received ATG. For 31 matched related and 33 alternate donor stem cell transplantation the overall treatment-related mortality was 3%. Projected disease-free and overall survival at 3 years for AML were the same at 83%, and for acute lymphoblastic leukemia were 65% and 78% respectively. For the marched related donors

the disease free survival was 77% and overall survival 87%, for alternative donors the disease free survival and overall survival were 71% and 84% respectively. Overall survival and disease free survival in patients without and with high-risk features were 100% versus 71% and 88% versus 68%, respectively. This combination therefore appears to be well tolerated and may offer better disease control than the standard FluBu.

2 STUDY RATIONALE

The combination of fludarabine and busulfan is the current standard of care for patients with myeloid malignancies (AML, CML and other myeloproliferative disorders, or MDS) undergoing allogeneic transplantation at HUMC. In this study we will be comparing in a randomized fashion the standard regimen to a regimen of fludarabine, busulfan and TBI.

2.1 Primary Objective

The primary objective is to compare the relapse rate at 1 year of patients with myeloid malignancies receiving each regimen.

2.2 Secondary Objectives

The secondary objective is to compare the toxicity of each regimen

3 INVESTIGATIONAL PLAN

3.1 Overall Design and Plan of Study

This is a single institution study of fludarabine and busulfan versus fludarabine, busulfan and low dose total body irradiation in patients undergoing allogeneic stem cell transplantation. A study population of 54 subjects will be enrolled from The John Theurer Cancer Center at Hackensack University Medical Center. Subjects who are eligible to receive allogeneic hematopoietic stem cell transplantation according to the eligibility criteria will be consented and enrolled. Subjects will be randomly assigned to receive one of 2 conditioning regimen: fludarabine and busulfan, or fludarabine busulfan and low dose total body irradiation (TBI). Subjects will be followed until 1 year post transplantation to assess the relapse rate in each arm and transplant-related toxicity

3.2 Patient Inclusion and Exclusion Criteria

3.2.1 Patient Inclusion Criteria

- 3.2.1.1 Diagnosis of acute myelogenous leukemia, chronic myelogenous leukemia, other myeloproliferative disorder, or myelodysplastic syndrome
- 3.2.1.2 Any stage of disease will be considered for transplantation
- 3.2.1.3 Have a suitable related or unrelated donor (Section 3.3)
- 3.2.1.4 Age ≥18 but <70 yrs
- 3.2.1.5 KPS of ≥70%
- 3.2.1.6 Recovery from all hematologic and non-hematology toxicities from previous therapies.

3.2.2 Patient Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study.

- 3.2.2.1 Diagnosis other than acute myelogenous leukemia, myeloproliferative disorder, or myelodysplastic syndrome
- 3.2.2.2 Chemotherapy or radiotherapy within 14 days of initiating treatment in this study with the exception of lenalidomide, decitabine, azacitidine, imatinib mesylate, dasatinib, nilotinib hydrochloride and hydroxyurea.
- 3.2.2.3 Prior dose-intense therapy requiring HSC support within 56 days of initiating treatment in this study
- 3.2.2.4 Uncontrolled bacterial, viral, fungal or parasitic infections
- 3.2.2.5 Uncontrolled CNS metastases
- 3.2.2.6 Known amyloid deposition in heart
- 3.2.2.7 Organ dysfunction
  - 3.2.2.7.1 LVEF <40% or cardiac failure not responsive to therapy
  - 3.2.2.7.2 FVC, FEV_1, or DLCO <50% of predicted and/or receiving supplementary continuous oxygen
  - 3.2.2.7.3 Evidence of hepatic synthetic dysfunction, or total bilirubin >2x or AST >3x ULN

3.2.2.7.4 Calculated creatinine clearance <20 ml/min

3.2.2.8 Karnofsky score <70%

3.2.2.9 Life expectancy limited by another co-morbid illness

3.2.2.10 Diagnosed or treated for another malignancy within 3 years of enrollment, with the exception of complete resection of basal cell carcinoma or squamous cell carcinoma of the skin, an in situ malignancy, or low-risk prostate cancer after curative therapy

3.2.2.11 Female subject is pregnant or breast-feeding (women) or unwilling to use acceptable birth control methods (men or women) for twelve months after treatment. Confirmation that the subject is not pregnant must be established by a negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test result obtained during screening. Pregnancy testing is not required for post-menopausal or surgically sterilized women.

3.2.2.12 Documented hypersensitivity to fludarabine or melphalan or to bortezomib, boron or mannitol or any components of the formulation

3.2.2.13 Patients unable or unwilling to provide consent

3.2.2.14 Myocardial infarction within 6 months prior to enrollment or has New York Heart Association (NYHA) Class III or IV heart failure (see section 8.4), uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities. Prior to study entry, any ECG abnormality at screening has to be documented by the investigator as not medically relevant

3.2.2.15 Patient has received other investigational drugs with 14 days before enrollment

3.2.2.16 Serious medical or psychiatric illness likely to interfere with participation in this clinical study

3.3 Donor Inclusion and Exclusion Criteria

3.3.1 Donor Inclusion Criteria:

3.3.1.1 HLA 6/6 (HLA-A, B, DrB1) related donor or 7/8 (HLA-A, B, C, DrB1) unrelated donor

3.3.1.2 Related donors will be evaluated in accordance with HUMC standard practice guidelines for the evaluation and management of allogeneic donors

3.3.1.3 Unrelated donors will be identified, evaluated, and managed in accordance with National Marrow Donor Program standards

3.3.1.4 KPS of ≥70%

3.3.1.5 Willing to donate bone marrow using standard techniques or peripheral blood HSC by leukapheresis

3.3.1.5.1 Have adequate veins for apheresis or agree to placement of a central venous catheter (femoral, subclavian) if donating peripheral blood HSC

3.3.2 Donor Exclusion Criteria

3.3.2.1 Identical twin

3.3.2.2 Female donors who are pregnant or breastfeeding

3.3.2.3 Infection with HIV or viral hepatitis (B or C)

3.3.2.4 Known allergy to filgrastim

3.3.2.5 Current serious systemic illness

3.3.2.6 Uncontrolled bacterial, viral, or fungal infection

3.3.2.7 Receiving experimental therapy or investigational agents

3.3.2.8 History of cancer other than treated basal cell cancer of the skin or carcinoma in situ of the cervix. Cancer treated with curative intent >5 yrs before donation will be reviewed on a case-by-case basis by the principal investigator

3.4 Patient Evaluation

Pre-transplant evaluation must be performed within 30 days of transplantation.

3.4.1 History with full details of the patient's prior treatments and responses

3.4.2 Physical exam with determination of Karnofsky score and findings related to underlying malignancy

3.4.3 Chemistry profile to include serum creatinine, AST, alkaline phosphatase, and bilirubin

3.4.4 CBC with differential

3.4.5 ABO and Rh

3.4.6 Serum pregnancy test, if female gender with child-bearing potential

3.4.7 HIV, Hepatitis B, Hepatitis C, CMV serology

3.4.8 Disease Staging:

3.4.8.1 Bone marrow aspiration and biopsy

3.4.8.2 Morphology

3.4.8.3 Cytogenetic evaluation

3.4.8.4 Fish study for common abnormalities associated with the disease being treated (if previously documented negative, need not be repeated to comply with this requirement).

3.4.8.5 Molecular testing for common abnormalities associated with the disease being treated

3.4.9 Pulmonary function tests with DLCO

3.4.10 MUGA scan or cardiac echo

3.4.11 EKG

3.5 Donor Evaluation

Pre-donation evaluation must be performed in accordance with HUMC Standard Operating Procedures for the evaluation and management of related HSC donors, or with NMDP Standard Operating Procedures for the evaluation and management of unrelated HSC donors.

3.6 HSC Product Evaluation

3.6.1 TNC, CD34+, and CD3+ cell counts

3.6.1.1 Bone marrow or PBSC products may be cryopreserved

3.7 Post-Transplant evaluation

3.7.1 Physical exam daily until hematological recovery and resolution of serious regimen-related complications

3.7.2 History and physical exam weekly through day 100 after transplantation, then at 6 months, 9 months, 12 months after transplantation.

3.7.2.1 Assessment and staging of acute and chronic GvHD will be performed and recorded at these visits and at least weekly through day +100 after transplantation

3.7.2.2 Once weekly assessment of toxicity in accordance with NCI toxicity guidelines from day-1 until resolution of all Grade 3/4 treatment-related toxicities, and then at days +28, +56, +84 (all ±7 days)

3.7.3 CBC daily from day 0 until ANC ≥500/ul on two sequential days after nadir reached (engraftment)

3.7.4 Chemistry profile 2 times per week until documentation of engraftment and then weekly through day +100 after transplantation

3.7.5 Chimerism evaluation at days +28, 56, and 84 (±7 days), at then at 6 months, 9 months, 12 months (±30 days) after transplantation. The Chimerism assessment will be performed in accordance with the protocol schedule of assessments. If a subject's insurance denies coverage, the assessment may be omitted

3.7.5.1 Peripheral blood samples will be separated to allow assessment of CD3+ cell chimerism

3.7.5.2 Chimerism studies will be obtained at time of relapse

3.7.5.3 Record of all medication administered during inpatient course

3.8 Post transplant re-staging of disease

3.8.1 Bone marrow aspirate and biopsy with cytogenetic evaluations will be obtained:

3.8.1.1 Day 84 (±7 days), at one year (±30 days), and whenever there is evidence of relapse

3.9 Study Medications

All medications used in this study are commercially available

3.9.1 Fludarabine:

Fludarabine is a fluorinated nucleotide analogue of the antiviral vidarabine. It acts as a purine antagonist antimetabolite. Synonyms: 2-F-ara-AMP. Bone-marrow suppression from fludarabine is dose-limiting, manifesting as neutropenia, thrombocytopenia, and anemia. Other adverse effects include fever, chills, cough, Dyspnea, pneumonia, gastrointestinal disturbances, stomatitis, edema, the tumor lysis syndrome, skin rashes, auto-immune hemolytic anemia and thrombocytopenia, and hemorrhagic cystitis. Neurological disturbances include peripheral neuropathy, agitation, confusion, visual disturbances, seizures, and coma; high doses have been associated with progressive encephalopathy, blindness, and death. Dosage should be reduced in renal impairment and fludarabine should not be given if creatinine clearance is less than 30 mL/minute. Intravenous fludarabine phosphate is rapidly dephosphorylated to fludarabine, which is taken up by lymphocytes and rephosphorylated to the active triphosphate nucleotide. Peak intracellular concentrations of fludarabine triphosphate are seen about 4 hours after a dose. Fludarabine has a bioavailability of about 50 to 65% after doses of the phosphate by mouth. Clearance of fludarabine from the plasma is triphasic with a terminal half-life of about 20 hours. Elimination is mostly via renal excretion: 60% of a dose is excreted in the urine. The pharmacokinetics of fludarabine exhibit considerable interindividual variation.

3.9.2 Busulfan:

The major adverse effect of busulfan with standard doses is bone-marrow suppression, manifest as leucopenia, thrombocytopenia, and sometimes, anemia. The nadir of the granulocyte count usually occurs after about 10 to 30 days with recovery occurring over up to 5 months, but busulfan has sometimes caused irreversible or extremely-prolonged bone-marrow depression. Hyperpigmentation is common, and in a few cases after long-term therapy may be part of a syndrome simulating Addison's disease. Rarely, progressive interstitial pulmonary fibrosis, known as `busulfan lung', can occur on prolonged treatment. Gastrointestinal disturbances are rare at usual therapeutic doses but may be dose-limiting where high doses are given before bone marrow transplantation. Other rare adverse effects include dry skin and other skin reactions, liver damage, gynaecomastia, cataract formation, and, at high doses, CNS effects including convulsions. Busulfan may result in impaired fertility and gonadal function. As with other alkylating agents, it is potentially carcinogenic, mutagenic, and teratogenic.

Busulfan is readily absorbed from the gastrointestinal tract and rapidly disappears from the blood with a half-life of 2 to 3 hours. It is extensively metabolized and excreted in the urine almost entirely as sulfur-containing metabolites. It crosses the blood-brain barrier.

Busulfan is an antineoplastic with a cell-cycle non-specific alkylating action unlike that of the nitrogen mustards, and having a selective depressant action on bone marrow. In small doses, it depresses granulocytopoiesis and to a lesser extent

thrombocytopoiesis but has little effect on lymphocytes. With larger doses, severe bone-marrow depression eventually ensues.

3.9.3 Rabbit antithymocyte globulin:

Antithymocyte globulins are antibodies, which act against lymphocytes, and in particular against T-cells, to produce suppression of cell-mediated immunity. Common adverse reactions include fever, chills, and skin reactions including rash, pruritus, and urticaria, which may be manifestations of hypersensitivity. Dyspnea, hypotension, chest, back or flank pain may indicate anaphylaxis, which can occur in up to 1% of patients. Rashes and arthralgia may represent serum sickness, especially in patients with aplastic anemia. Use with other immunosuppressants may reduce the incidence or severity of hypersensitivity but increase the risk of acquired systemic infections, such as CMV or herpes simplex. Enhanced immunosuppression may also increase the incidence of post-transplant lymphoproliferative disease or other malignancies. Leucopenia and thrombocytopenia are also common. Although usually transient, dosage adjustment may be necessary if they become severe or prolonged, and if unremitting, they may warrant stopping therapy. Other adverse effects include headache, abdominal pain, gastrointestinal disturbances, hypertension, peripheral edema, asthenia, hyperkalaemia, and tachycardia. Nephrotoxicity has been reported.

3.10 Outline of Treatment Plan

Eligible patients who have signed informed consent will undergo pre-transplant evaluation and clearance as per current transplant program standard operating procedures. Patients will be admitted to Hackensack University Medical Center for the administration of the fludarabine, busulfan, TBI and for the transplant procedures

Table 1: Treatment Schema for Conditioning Regimen

	Day of Transplant											
	-6	-5	-4	-3	-2	-1	0	+1	+3	+6	+9	+11
Fludarabine 40mg/m2	X	X	X	X								
Busulfan 130 mg.m2	X	X	X	X								
rATG				X	X	X						
TBI 200 cGY (as randomized)						X/ X						
Tacrolimus					X→							
Stem cell infusion							X					
Methotrexate 5 mg/m2								X	X	X		X
Filgrastim 5 ug/kg											X→	

3.10.1 Conditioning Regimens

Eligible patients who have signed informed consent will be randomized to treatment arm A (Flu-Bu) or treatment arm B (Flu-Bu-TBI).

3.10.2 Treatment arm A:

3.10.2.1 Patients must be admitted to HUMC prior to the start of the fludarabine and will not be discharged until engraftment has occurred.

3.10.2.2 Fludarabine will be administered at a dose of 40/mg/m2 IV daily for 4 days starting on transplant day -6.

3.10.2.3 Busulfan will be administered immediately following the fludarabine at a dose of 130 mg/m2 IV daily for 4 days starting on transplant day -6.

3.10.2.4 Patients will also receive rabbit antithymocyte globulin (Thymoglobulin) at a dose of 0.5 mg/kg IV on day -3, and 1.5 mg/kg on day -2 and 2 mg/kg on day -1

3.10.2.5 Hematopoietic cells will be infused on day 0

3.10.2.6 Graft versus host disease (GVHD) prophylaxis will consists of tacrolimus 0.03 mg/kg (or 0.015 mg/kg for age ≥65) using ideal body weight, IV total daily dose starting on transplant day -2 and adjusted based on blood levels. Methotrexate at a dose of 5 mg/m2 IV will be administered on transplant days +1, +3, +6 and +11

3.10.2.7 Dose adjustment for the fludarabine, busulfan and antithymocyte globulin will be as follows:

3.10.2.7.1 If patient weighs less than 100% of ideal body weight (IBW), dosing is based on actual body weight

3.10.2.7.2 If patient weighs 120-150% of IBW, dosing is based on adjusted body weight (ABW)

3.10.2.7.3 If patient weighs greater than 150% of IBW, actual weight will be capped at 150% of ideal body weight, and this will be used in the adjusted body weight formula

3.10.2.8 Corrected body weight formula: ABW= IBW + [(0.25) x (actual BW-IBW)]

3.10.3 Treatment arm B:

3.10.3.1 Patients must be admitted to HUMC prior to the start of the fludarabine and will not be discharged until engraftment has occurred.

3.10.3.2 Fludarabine will be administered at a dose of 40/mg/m2 IV daily for 4 days starting on transplant day -6.

3.10.3.3 Busulfan will be administered immediately following the fludarabine at a dose of 130 mg/m2 IV daily for 4 days starting on transplant day -6.

3.10.3.4 Total body irradiation will be given in 2 fractions of 200 CGY (total 400 CGY) on day -1.

3.10.3.5 All patients in treatment arm B will also receive rabbit antithymocyte globulin (Thymoglobulin) at a dose of 0.5 mg/kg IV on day -3, and 1.5 mg/kg on day -2 and 2 mg/kg on day -1.

3.10.3.6 Hematopoietic cells will be infused on day 0.

3.10.3.7 Graft versus host disease (GVHD) prophylaxis will consists of tacrolimus 0.03 mg/kg (or 0.015 mg/kg for age ≥65) using ideal body weight, IV total daily dose starting on transplant day -2 and adjusted based on blood levels. Methotrexate at a dose of 5 mg/m2 IV will be administered on transplant days +1, +3, +6 and +11.

3.10.3.8 Dose adjustment for the fludarabine, busulfan and antithymocyte globulin will be as follows:

3.10.3.8.1 If patient weighs less than 100% of ideal body weight (IBW), dosing is based on actual body weight.

3.10.3.8.2 If patient weighs 120-150% of IBW, dosing is based on adjusted body weight (ABW).

3.10.3.8.3 If patient weighs greater than 150% of IBW, actual weight will be capped at 150% of ideal body weight, and this will be used in the adjusted body weight formula.

3.10.3.9 Corrected body weight formula: ABW= IBW + [(0.25) x (actual BW-IBW)]

3.10.4 Stem cell infusion:

Day 0 for purposes of methotrexate administration is defined as the day the HSC infusion is completed. The infusion of peripheral blood stem cells will be done in accordance with the Blood and Marrow Transplant program standard operating procedures

3.10.5 Graft versus host disease (GVHD) prophylaxis:

GvHD prophylaxis consists of tacrolimus 0.03 mg/kg (or 0.015 mg/kg for age ≥65) using ideal body weight, IV total daily dose starting on transplant day -2 and adjusted based on blood levels. Methotrexate at a dose of 5 mg/m2 IV will be administered on transplant days +1, +3, +6 and +11

3.10.6 Supportive care after transplantation

Supportive care including transfusions, hydration and prophylactic antibiotics will be provided as per current transplant program standard operating procedures.

3.10.7 Post-transplant cytokine administration

Filgrastim will be administered at a dose of 5 mcg/kg (rounded to vial size) every day starting on day+9 until neutrophil engraftment

3.10.8 GvHD management

Management of GvHD is not defined in this protocol. Patients may be treated in accordance with usual practices and are encouraged to enroll into clinical studies of the management of these complications of transplantation Supportive care including

transfusions, hydration and prophylactic antibiotics will be provided as per current transplant program standard operating procedures.

4 ADVERSE EVENTS

4.1 Definitions

4.1.1 Adverse Event Definition

An adverse event (AE) is any untoward medical occurrence in a patient administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. An adverse event can be any unfavorable and unintended sign (eg, including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the drug, whether or not it is considered to be drug related. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of drug.

4.1.2 Serious Adverse Event Definition

A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- 4.1.2.1 Results in death.
- 4.1.2.2 Is life-threatening. Life-threatening means that the patient was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- 4.1.2.3 Requires inpatient hospitalization or prolongation of existing hospitalization. Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered AEs if the illness or disease existed before the patient was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (eg, surgery performed earlier than planned).
- 4.1.2.4 Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a persons' ability to conduct normal life functions.
- 4.1.2.5 Is a congenital anomaly/birth defect.
- 4.1.2.6 Is an important medical event. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Clarification should be made between the terms "serious" and "severe" since they ARE NOT synonymous. The term "severe" is often used to describe the intensity (severity) of a

specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is NOT the same as "serious," which is based on patient/event outcome or action criteria described above and are usually associated with events that pose a threat to a patient's life or functioning. A severe adverse event does not necessarily need to be considered serious. For example, persistent nausea of several hours duration may be considered severe nausea but not an SAE. On the other hand, a stroke resulting in only a minor degree of disability may be considered mild, but would be defined as an SAE based on the above noted criteria. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

4.2 Procedures for AE and SAE Reporting

The Principle Investigator-sponsor must report all serious adverse events (SAE) regardless of relationship with any study drug or expectedness to the IRB as required by the institution.

4.3 Intensity for each adverse event, including any lab abnormality, will be determined by using the NCI CTCAE, version 3.0 (or later version), as a guideline, wherever possible. The criteria are available online at ***http://ctep.cancer.gov/reporting/ctc.html***.

4.4 Assessment of Toxicity

4.4.1 Common Terminology Criteria for Adverse Events (CTCAE) will be used for the assessment and grading of all toxicities experienced by patients enrolled into this study (http://ctep.cancer.gov/forms/CTCAE_Index.pdf)

4.4.1.1 If the nature of the adverse experience is listed in the CTCAE, the maximum grade and time of maximum grade will be reported.

4.4.1.2 If the adverse experience is not listed on the NCI CTG Expanded Toxicity Criteria Appendix D, report the toxicity grade using the following criteria.

4.4.1.2.1 **Grade 1 = Mild:** an adverse experience which is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.

4.4.1.2.2 **Grade 2 = Moderate:** an adverse experience which is sufficiently discomforting to interfere with normal everyday activities.

4.4.1.2.3 **Grade 3 = Severe:** an adverse experience which is incapacitating and prevents normal everyday activities.

4.4.1.2.4 **Grade 4 = Life Threatening:** an adverse experience which places the patient at immediate risk of death.

4.5 **Assessment of Causality**

4.5.1 Every effort should be made by the investigator to explain each adverse experience and assess its relationship, if any, to study drug treatment. Causality should be assessed using the following categories: Not Related, Unlikely, Suspected (*Reasonable Possibility)*, Probable.

4.5.1.1 **Not related:** The adverse experience is definitely not related to the test drug.

4.5.1.2 **Unlikely:** There are other, more likely causes and the drug is not suspected as a cause.

4.5.1.3 **Suspected (reasonable possibility):** A direct cause and effect relationship between the drug and the adverse experience has not been demonstrated but there is a reasonable possibility that the experience was caused by the drug.

4.5.1.4 **Probable:** There probably is a direct cause and effect relationship between the adverse experience and the study drug.

4.5.2 The degree of certainty with which an adverse experience is attributed to drug treatment (or alternative causes, e.g. natural history of the underlying diseases, concomitant therapy, etc.) will be determined by how well the experience can be understood in terms of one or more of the following:

4.5.2.1 Known pharmacology of the drug

4.5.2.2 Reaction of similar nature being previously observed with this drug or class of drug. The experience having often been reported in literature for similar drugs as drug related e.g. skin rashes, blood dyscrasia. The experience being related by time to drug ingestion terminating with drug withdrawal (dechallenge) or reproduced on rechallenge

4.6 Follow-up of Adverse Experiences

4.6.1 Patients with Grade 3/4 adverse experiences will be actively followed until the event has subsided (disappeared) or until the condition has stabilized.

4.6.2 Adverse events, both serious and non-serious, and deaths that occur during the patient's study participation will be recorded in the source documents. All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es)

5 STATISTICAL EVALUATION

5.1 Primary Objective

The primary objective of this single institution randomized Phase III trial is to compare the 1-year relapse rate of myeloid malignancy in patients receiving two different conditioning regimens. In this study, subjects will be randomly assigned to one of 2 conditioning regimens: fludarabine and busulfan or fludarabine, busulfan and low-dose total body irradiation. The myeloid malignancies include acute myeloid leukemia (AML), chronic myeloid leukemia (CML) and other myeloproliferative diseases, and myelodysplastic syndromes (MDS).

Primary endpoint will be the 1-year event free survival (EFS) for the two treatment groups, where the event is relapse or progression. Patients are considered a failure with respect to EFS if they experience disease relapse or progression. The time to this event is the time from transplant to relapse or progression. Subjects alive without confirmed disease progression will be censored at the time of last disease evaluation. Patients who die without evidence of disease relapse or progression will be censored at time of death and death will not be treated as failure for analysis of this primary endpoint.

5.2 Secondary Endpoints

Secondary endpoints will include:

5.2.1 Overall survival (OS): Defined as time from the first dose of administration to death from any cause.

5.2.2 Overall response rates: Defined as the composite endpoint of response to treatment which includes Complete Response (CR), Partial Response (PR), stable disease (SD) as defined in International Response Criteria. We will also analyze Complete Response rate.

5.2.3 Univariate analysis of the risk of progression/relapse and mortality: In addition, multivariate analysis of the risk of progression/relapse and overall mortality will be conducted to assess influence of variables measured after the start of treatment.

5.2.4 Regimen-related toxicity: Graded and presented in a descriptive nature.

Descriptive analysis of baseline characteristics and demographics in this two-treatment arms study will be performed in the following manner. Continuous measurements will be summarized as mean (SD) or median (inter-quartile range) based on whether or not the data come from a normal distribution as validated by Shapiro-Wilks test of normality. Categorical measurements will be summarized as frequency (percentage). Proportion of overall survival will be estimated by the Kaplan-Meier product limit method. The univariate probability of the relapse and treatment–related mortality (TRM) will be calculated using cumulative incidence function.

5.3 Accrual, Registration and Follow-up

The targeted sample size is 54 subjects. It is estimated that four years of accrual will be necessary to enroll this number of subjects. About 50 patients (49-52) underwent allogeneic transplantation at this center, indicating that an appropriate number of subjects will be available to complete this study in the time frame anticipated. Subjects will enroll uniformly over the accrual period. The randomization will be stratified by relapse risk status (high versus low). Low relapse will include: AML CR1 and CML chronic phase. All other AML, MPD and MDS patients will be considered high relapse risk. An AML CR1 patient with a history of MDS will be considered high relapse risk. All patients who are Flt3/ITD positive at any time will be considered high relapse risk. Upon establishing eligibility, subjects will be randomized in equal numbers to the FluBu and FluBuTBI arms using permuted blocks within strata.

All subjects will be followed for one year from time of transplantation, during which they will be monitored for the effects of treatment through regular clinic visits. Additional follow-up data beyond one year of progression-free survival will be obtained from HUMC Cancer Center Database.

5.4 Sample Size and Power Calculations

The main objective is to compare the relapse-free surviving proportions at 1 year in myeloid malignancy patients who are randomized to either FluBuTBI or FluBu conditioning regimen.

In examining the time to relapse, we consider an analysis of the proportion surviving without relapse/progression at the 1 year endpoint. A comparison of this event between the two treatment arms will be conducted using log-rank test statistics at the 5% level of significance. Based on this statistic, the calculation of sample size was obtained using PASS 2008. According to the results from previous studies [De Lima et al], the 1-year relapse rate in patients with myeloid malignancies being treated with FluBu is 34%. We posit that when the FluBuTBI regimen is used the relapse rate will be reduced to 13.6%, which is 40% of the relapse risk in the FluBu regimen arm. Then, a one-sided log-rank test will be used to examine evidence for a reduction in disease relapse. For the nominal power of 80%, significance level of 5%, 4 year accrual, 1 year follow-up and 10% drop out rate in both FluBuTBI and FluBu treatment arm, 52 patients (26 per arm) will be required to detect the 20.4 difference (60% reduction in relapse rate). This calculation achieved 80.06%. To adjust for balanced samples within the risk status, the study will enroll a maximum of 54 patients (27 per arm).

5.5 Efficacy Analysis

This is a phase III study comparing one-year relapse rate after allogeneic HSCT with fludarabine, busulfan and total body irradiation regimen and fludarabine and busulfan regimen in patients with a diagnosis of myeloid malignancies.

5.6 Statistical Hypothesis

The null hypothesis is that the 1 year relapse rate is 34%. It is the goal of this study to show that when fludarabine, busulfan and total body irradiation is used as the regimen the risk of relapse is 40% that of the flubudarabine and busulfan regimen. Then, we are seeking a relapse rate of 13.6 % in the in the FluBuTBI regimen arm which is less than that in FluBu regimen arm. Thus, we will evaluate the hypotheses

$H_O: \theta_A \leq \theta_B$

$H_A: \theta_A > \theta_B$

where θ_A= rate of relapse in Arm A (FluBu) which is assumed to be 0.34,

θ_B= rate of relapse in Arm B (FluBuTBI).

Due to the lack of homogeneity in the outcome as a result of risk status (low versus high), it will be useful to stratified on risk status. Thus, a one-sided log-rank test stratified on risk status will be conducted to ascertain if FluBuTBI reduces the relapse rate from that in over FluBu using a 5% level of significance.

5.7 Primary Endpoint

The primary analysis will include all randomized subjects, classified according to their randomized treatment allocation by the *intent-to-treat* principle. The analysis of relapse or disease progression is planned at one year after accrual is completed. The two regimen arms will be compared utilizing a one-sided log rank test stratified on risk status, and using a level significance level of 0.05.

5.8 Secondary Endpoints

5.8.1 Secondary endpoints will include:

5.8.1.1 Overall response rates: Defined as the composite endpoint of response to treatment which includes Complete Response (CR), Partial Response (PR), stable disease (SD) as defined in International Response Criteria. We will also analyze Complete Response rate.

5.8.1.2 Overall survival (OS): Defined as time from the first dose of administration to death from any cause.

5.8.1.3 Univariate analysis of the risk of progression/relapse and mortality: In addition, multivariate analysis of the risk of progression/relapse and overall mortality will be conducted to assess influence of variables measured after the start of treatment.

5.8.1.4 Regimen-related toxicity: Graded and presented in a descriptive nature.

5.8.2 Overall Survival

The event is death from any cause. The time to this event is the time from randomization to death, loss to follow-up or the end of the study, whichever comes first. Patients alive at the time of last observation are considered censored. The Kaplan-Meier estimate of survival will be estimated separately for each treatment-

group and risk status. A log-rank test stratified on risk status, conducted at a one-sided significance level of 0.05 analogous to the analysis of relapse risk described above.

5.8.3 Overall Response to Treatment

A comparative analysis of the response rate to the transplant between the two conditioning regimen will also be performed using the incident (CR, PR, SD) as the overall response. In addition the CR rate between the treatment arms will also be analyzed. The comparison of the response rate to the transplant with respect to the overall and CR component be performed using Mantel-Haenszel Test stratified on relapse risk status.

5.8.4 Event-Free Survival

The event is death from any cause or relapse/disease progression. The time to this event is the time from randomization to death, relapse or disease progression, loss to follow-up or the end of the study, whichever comes first. Patients alive at the time of last observation are considered censored. The Kaplan-Meier estimate of survival will be estimated separately for each treatment-group and risk status. A one-sided log-rank test stratified on risk status will be conducted at the 5% level of significance, analogous to the analysis of relapse risk described above.

5.8.5 Association of Prognostic Factors and Risk of Progression/Relapse and Mortality

A comparative analysis of risk outcomes relapse/progression, TRM, and overall Mortality will be conducted while adjusting for imbalance in other risk factors using a Cox proportional hazards model (1). To fit the multivariate model, a stepwise backward selection procedure will be used while considering the type of conditioning regimen (FluBuTBI versus FluBu), relapse risk status (low risk, high risk), age at transplant and Karnofsky performance score (<90 versus ≥ 90) , donor-gender, CMV, HLA match grade, and stem cell source as potential covariates. Covariates yielding a p-value of 0.05 or less will be an indication of statistical significance. Graft-versus host disease (GVHD) will be entered as a time-dependent covariate. Both acute GVHD and chronic GVHD will be considered as subtypes of GVHD. An examination of the goodness-of-fit will be performed using Grambsch-Therneau and Martingale residual plots (2) and lowess smooth of Cleveland (3). The proportionality assumption for Cox regression will be validated by introducing a time-dependent covariate for each risk factor and outcome. Since BM blast cell count, presence of peripheral blood blast, and whether or not the patient is in CR at transplant are collinear only one variable will be used in single model fitting attempt. Thus, three different models will be considered when examining the association risk factors and disease relapse and OS. The results of this analysis will be presented in terms of relative risks (RR) along with the corresponding p values for each covariate.

5.8.6 Safety Analysis

Safety Analysis will be performed on all patients who have at least one dose of medication on either treatment arms over the course of this study. The severity of the toxicities will be graded according to the NCI CTCAE v3.0 whenever possible. Events during the first 100 days after transplantation will be considered possibly related to the transplant for this analysis. Regimen-related toxicity will be graded and presented in a descriptive nature as incidence rates and the corresponding 95% confidence intervals.

5.8.6.1 Safety Monitoring Endpoints

The incidence of toxicities of grade 3 or higher toxicities (CTCAE version 3.0), the incidence of probable viral fungal and bacterial infections, and the incidence of treatment-related morality, i.e., from causes other than relapse or progression, will be recorded for each patient at set intervals over the course of the study. Safety data will be described in a variety of ways, both graphical and tabular, and incidence will be compared across time points and treatment arms. The Data and Safety Monitoring Board will be presented with a comprehensive semi-annual report that will contain both solicited and unsolicited adverse event reports.

5.9 Discontinuation from study

5.9.1 Withdrawal of patients

A patient must be withdrawn from the study under the following circumstances:

5.9.1.1 Consent withdrawal at the patient's own request or at the request of their legally authorized representative;

5.9.1.2 Toxicity or adverse event requiring treatment that would, in the investigator's opinion, interfere with study endpoints

5.9.1.3 Safety reasons requiring discontinuation as determined by the physician(s) caring for the patient

5.9.1.4 Significant deviation from inclusion/exclusion criteria, in the opinion of the investigator;

5.9.1.5 If, in the investigator's opinion, continuation in the study could be detrimental to the patient's well-being;

5.9.1.6 Progression of disease (POD) after CR or PR.

When possible, subjects who are taken-off study or withdraw participation should undergo End-of-Study procedures. In addition, patients will be followed for a period of 28 days following the day of discontinuation for collection of study related adverse events.

5.9.2 Replacement of patients

Patients withdrawn after treatment group assignment may be replaced unless the patient discontinued due to as adverse event or the patient met a study endpoint (e.g., disease progression).

5.10 Stopping Rules

If the non-relapse mortality rate in the experimental group receiving TBI within the first 3 month post exceeds 20% then the study will be stopped. It is assumed that the NRM in the standard FluBu conditioning regimen is 10%. Resumption of patient accrual will only be permitted after review of interim results by the Institutional Review Board and the Data Safety Monitoring Board

5.11 Monitoring Compliance

Patients enrolled into the study will be monitored for treatment actually received. Failure to comply with study conditioning regimen would first trigger an intervention to improve compliance.

5.12 Data Management and Analysis

Case report forms will be created for management of data collected during this study. A database in Access will be created based on the case report forms. All study data will be imported into SAS and data management will be utilized to flag, and generate queries on out of range data issues until they are resolved. All analysis will be performed using SAS software version 9.2 (SAS Institute Inc. Cary, NC).

6 ADMINISTRATIVE CONSIDERATIONA

6.1 Patient and Donor Information and Informed Consent

The patient must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to him or her. Informed consent documents that include both information about the study and the consent form will be given to the patient. Related donor informed consent will be obtained in accordance with Standard Operating Practice. This document will contain all required regulatory elements. The document must specify who informed the patient and the donor. Informed consent for unrelated donors will be in accordance with NMDP standards and procedures and will be obtained by the donor center.

After reading the informed consent document, the patient and donor must give consent in writing. The patient's consent must be confirmed at the time of consent by the personally dated signature of the person conducting the informed consent discussions. A copy of the signed consent document must be given to the patient or the patient's legally authorized representative. The investigator will retain the original signed consent documents in the medical record. The investigator will not undertake any measures specifically required only for the clinical study until valid consent has been obtained.

6.2 Institutional Review Board Review

This study will not be initiated until it is reviewed and approved by the IRB. Any modifications to the study must be reviewed and receive written approved by the IRB before they can be implemented. Amendments that are administrative in nature do not require IRB approval but will be submitted to the IRB for information purposes.

6.3 Data and Safety Monitoring Board

The HUMC DSMB is responsible for developing and enacting procedures to monitor safety of participants in protocols that it oversees. They provide multidisciplinary, independent oversight of research studies conducted by HUMC staff and or affiliates, focusing on assuring integrity of research and safety of subjects. The DSMB has the ability to require protocol modifications related to participant safety and to recommend suspension of termination to the IRB and institutional official of any research protocols that fall within its jurisdiction. The DSMB may request that HUMC's Corporate Compliance Department to conduct a periodic audit to assure that data are being collected and recorded according to the protocol. The investigator will submit monitoring reports that include current enrollment data, adverse event summary data, and any other data requested by the DSMB.

The DSMB will meet monthly to review the trial progress, adverse event data, and any relevant information such as significant amendments or reviews from IRB submitted by the principal investigator.

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