THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Abstract Page

A randomized study of once daily Fludarabine-Clofarabine vs Fludarabine alone combined with IV Busulfan followed by allogeneic hemopoietic stem cell transplantation for AML and MDS
2011-0628

Core Protocol Information

Short Title:	Fludarabine-IV Busulfan ± Clofarabine and allogeneic hematopoietic stem cell transplantation for AML and MDS
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Full Title:	A randomized study of once daily Fludarabine-Clofarabine vs Fludarabine alone combined with IV Busulfan followed by allogeneic hemopoietic stem cell transplantation for AML and MDS
Protocol Phase:	Phase III
Version Status:	Activated -- Closed to new patient entry as of 07/16/2018
Version:	16
Document Status:	Final

Abstract

Objectives:

Primary Objectives

1. To determine if the preparative regimen of Fludarabine (Flu), Clofarabine (Clo) plus Busulfan (Bu) will produce superior progression free survival compared to Fludarabine and Busulfan alone in a phase III randomized controlled trial in patients with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) receiving allogeneic stem cell transplantation.

2. Determine the rate of engraftment, toxicity, relapse rate, graft-vs-host disease (GvHD), progression-free survival (PFS) and overall survival (OS) with each regimen.

Rationale: (Be as concise as possible)

In this phase 3 randomized controlled trial, we will determine if the Bu-Flu-Clo regimen improves progression free survival compared to the Flu-IV Bu regimen. In the current study we propose to administer IV Bu at a PK-guided dose that yields an AUC of 6000 µMol-min (±5%) for patients up to age 60 and at a systemic exposure of an AUC of 4,000 µMol-min (±5%) for patients ages 61-70 years or with impaired performance status. The pharmacological parameters will be calculated using a pharmacokinetic model derived from our previous data base on the pharmacokinetics of IV Bu analyzed with the ADAPT II program for clinical pharmacokinetics. Bu will be given in combination with Flu and Clo as outlined below. The drugs are given daily for 4 days as preparation for bone marrow or peripheral blood stem cell transplantation for patients with either AML or MDS. The targeted AUC of 6000 µMol-min (and 4,000 µMol-min, respectively) are based on our cumulative experience with the relevant systemic exposure doses in the recently completed and currently ongoing clinical transplant protocols,

Busulfan pharmacogenetic studies. The main cytotoxic actions of busulfan is thought to be through DNA inter-strand cross-link formation and of Clo and Flu through inhibition of DNA damage repair through interference with DNA polymerase, Deoxy-Cytidine kinase and ribonucleotide reductase, respectively, as well as through induction of apoptosis through mitochondrial pathways. To investigate whether these biochemical events, and other events linked to Bu resistance/drug cytotoxicity and development of GvHD can be correlated with treatment outcome, we intend to collect blood from patients and study the *in vitro* alkylating effects of busulfan as well as the DNA damage repair inhibition of Clo and Flu. If possible, we also intend to study cytokine activation/release in conjunction with and following the transplant through weekly blood samples during the first month post transplantation. These samples will be analyzed for both serum cytokine levels and for intracellular cytokine activation. We anticipate to elucidate a pattern of cytokine activation that will herald the onset of both toxic events and those of graft vs host disease after the transplant.

Eligibility: (List All Criteria)

Inclusion:

1) Patients must have one of the following hematologic malignancies: a) Acute myeloid leukemia (AML) any stage and cytogenetic risk-group with the only exception being that patients with AML and favorable cytogentics (t(8;21, inv 16, or t(15;17) who achieve complete remission with one course of induction chemotherapy are not eligibile. Patients with treatment related AML are eligible. b) Myelodysplastic syndromes (MDS) with intermediate or high risk International Prognostic Scoring System score (IPSS scores) or treatment related MDS. Patients with low risk MDS are eligible if they fail to respond to hypomethylating agent therapy such as azacidine or decitabine.
2) Age 3-70 years old. Eligibility for pediatric patients will be determined in conjunction with an MDACC pediatrician.
3) Performance score of >/= 60 by Karnofsky or PS 0 to 2 (ECOG) (age > 12 years), or Lansky Play-Performance Scale >/= 60 or greater (age <12 years).
4) Negative Beta HCG test in a woman with child bearing potential, defined as not post-menopausal for 12 months or no previous surgical sterilization. Women of child bearing potential must be willing to use an effective contraceptive measure while on study.
5) Adequate major organ system function as demonstrated by: Left ventricular ejection fraction of at least 40%.
6) Pulmonary function test (PFT) demonstrating a diffusion capacity of least 50% predicted. For children </=7 years of age who are unable to perform PFT, oxygen saturation >/=92% on room air by pulse oximetry.
7) Creatinine < 1.5 mg/dL. If question about renal function discuss with study chairman and do 24 hour creatinine clearance (clearance should be >50 ml/min).
8) Bilirubin < to 2.0 x normal (except Gilbert's Syndrome). SGPT (ALT) < 200. No evidence of chronic active hepatitis or cirrhosis.
9) Histocompatible stem cell donor: Patients must have an HLA matched related or unrelated donor (HLA A, B, C and DR) willing to donate for allogeneic hematopoietic transplantation. High resolution allele level typing is required for donors other than genotypically identical siblings.
10) No uncontrolled infection. Protocol PI or designé will be final arbiter if there is uncertainty regarding whether a previous infection is controlled on appropriate (antibiotic) therapy.
11) Patient or patient's legal representative, parent(s) or guardian able to sign informed consent.

Exclusion:

1) Positive for HIV, HBsAg, HCV or other viral hepatitis or cirrhosis from any cause.
2) Prior allogneic or autologous stem cell transplant using a myeloablative busulfan or total body radiation containing conditioning regimen defined as busulfan-based using a total dose of >/=12 mg/kg given by mouth or >/=10 mg/kg given IV; or a total-body irradiation (> 4 Gy).
3) Active or prior CNS leukemia, unless in complete remission for at least 3 months.
4) Previous therapeutic XRT to the liver as part of involved-field radiation.
5) History of serious chronic mental disorder or drug-abuse accompanied by documented problems of compliance with therapeutic programs.
6) Lack of care-giver for the early (100-day) post-transplant period.

Are patients <18 years of age eligible to participate in this study? (●) Yes ( ) No

Studies that include children must meet the criteria for inclusion.

http://www.fda.gov/ohrms/dockets/AC/04/briefing/4028B1_05_NIH-Inclusion%20of%20Children.doc

http://www.hhs.gov/ohrp/policy/populations/children.html

Are participants >65 years of age eligible to participate in this study? (●) Yes ( ) No

Are pregnant women eligible to participate in this study? ( ) Yes (●) No

Will the recruitment population at M. D. Anderson include persons who are incarcerated at time of enrollment (e.g., prisoners) or likely to become incarcerated during the study?

( ) Yes (●) No

Disease Group:

Blood And Marrow Transplantation, Leukemia

Treatment Agents/Devices/Interventions:

ATG, Busulfan, Clofarabine, Fludarabine

Proposed Treatment/Study Plan:

Is treatment assignment randomized? (●) Yes ( ) No

Is this a blinded or double-blinded study? ( ) Yes (●) No

Allogeneic graft.

Peripheral blood (PB) or bone marrow (BM) progenitor cells may be used in this study.

Preparative Regimen.

Patients will be randomized to received either Flu/Bu or Flu/Clo/Bu and further stratified based on disease status, in complete remission (CR) or not in CR (NCR), at time of protocol entry/start of therapy.

Prior to initiating chemotherapy in this study, all toxicities from prior systemic chemotherapy must be resolved at least to grade 1. Flt3 or TKI inhibitors as well as intra-thecal therapy, nonmyelosuppressive agents, low dose cytarabine, hydroxyurea are permitted if indicated to control active leukemia, but must be stopped at least 5 days prior to administering the PK-test dose of IV Busulfan to avoid pharmacologic interference with IV Bu.

Acetaminophen should not be used between D-10 (starting 24 hours before the test dose of IV Bu) and D0. Other drugs known to interfere with the metabolism of Flu and/or Bu should not to be concomitantly used during the chemotherapy administration up to and including the day of transplantation. day following the stem cell transplant procedure.

Busulfan test dose:

The Busulfan test dose can be administered within 10 days prior to admission as an outpatient or as an inpatient.

Pharmacokinetic-guided (PK-guided) treatment: The Bu “test dose” of 32 mg/m^2 will be based on actual body weight. This Bu dose will be given IV over 45 minutes (for patients up to age 60) and over 60 min (for patients ages 61-70) by controlled-rate infusion pump.

Busulfan adjusted dose determined to achieve a systemic exposure represented by an average daily AUC of 6000 µMol-min ± 5% for the entire 4-day treatment period is administered to all patients up to age 60 who have ECOG performance status 0 or 1 or Karnofsky/Lansky 90-100. The target AUC is 4,000 µMol-min ± 5% for patients ages 61-70 and younger patients with ECOG performance status 2 or Karnofsky 60-80. If pharmacokinetic analysis cannot be completed for any reason, Bu will be given in a dose of 130 mg/m^2 dose (for the target AUC 6000) and 100 mg/m2 (for target AUC 4000).

Fludarabine/ Clofarabine/ Busulfan

Fludarabine administration:

Flu is administered at a dose of 10 mg/m^2 in 100 ml of NS on each of four (4) consecutive days (days -6 through -3). Intravenous fluids should be administered at a rate of that is $\geq$ 65 mL/m2/hour starting the evening before the start of Flu, through twenty-four (24) hours after the last dose of Bu.

Clofarabine administration:

Clo will be dosed per actual body weight/actual body surface area. Clo is administered at a dose of 30 mg/m^2 diluted in NS to produce a final concentration of 0.4 mg/mL, and infused on each of four (4) consecutive days (days -6 through -3). The doses of Clo are to follow immediately after Flu administration and prior to Bu on days -6 to -3 respectively. Intravenous fluids should be administered at a rate of that is ≥ 65 mL/m2/hour starting the evening before the start of this chemotherapy, through twenty-four (24) hours after the last dose of Bu.

Busulfan administration:

The PK-guided daily high-dose Bu dose(s) will be started immediately upon completion of the daily Clo dose. The Bu doses will be diluted in normal saline or 5% dextrose in water and administered daily by controlled rate infusion pump. Bu is administered at the dose calculated to achieve a systemic exposure dose of 6000 µMol-min in normal saline IV every twenty-four (24) hours for four (4) consecutive days (days -6 to -3), starting immediately after the completion of Clo. The Bu dose on day -6 to –3 will be based on the pharmacokinetic studies to target an AUC of 4,000 µMol-min ± 5% for patients 61-70 years of age or younger patients with ECOG performance status 2 or Karnofsky 60-80. If pharmacokinetic analysis cannot be completed for any reason, Bu will be given in a dose of 130 mg/m^2 dose.

The PK adjusted dose of Bu=Target AUC x Bu mol. wt (0.2463) x Bu gross the measured clearance normalized to body surface area (L/min) + the dose remaining in the IV line (priming dose).

Fludarabine/ Busulfan

Fludarabine administration:

Flu is administered at a dose of 40 mg/m^2 in 100 ml of NS on each of four (4) consecutive days (days -6 through -3). Intravenous fluids should be administered at a rate of that is ≥ 65 mL/m2/hour starting the evening before the start of Flu, through twenty-four (24) hours after the last dose of Bu.

Busulfan administration:

The PK-guided daily high-dose Bu dose(s) will be started immediately upon completion of the daily Flu dose. It is administered identically to the Fludarabine/clofarabine/busulfan group.

D-3 to D-1 Anti-thymocyte globulin administration**:**

Patients in both groups who receive a graft from an unrelated donor will receive Thymoglobulin; 0.5 mg/kg on day –3, 1.5 mg/kg on day –2 and 2.0 mg/kg on day –1. On day -3, this will be administered after the chemotherapy is complete (see Treatment Scheme below).

Stem Cell infusion

Fresh of cryopreserved bone marrow or peripheral blood progenitor cells will be infused on day 0. The goal is to infuse 5 X 10^6 CD34+ cells/kg if PB or >3.0 X 10^8 marrow mononuclear cells/kg if BM. Premedication for the infusions will be per standard SCTCT department procedures.

Prophylaxis and Supportive Care as per standard practice in patients receiving allogeneic transplant and SCTCT Guidelines

GvHD with Tacrolimus and Mini Methotrexate with dose adjustment as clinically indicated.
Tacrolimus will be administered at starting dose of 0.015 mg/kg (ideal body weight) as a 24 hour continuous infusion daily adjusted to achieve a therapeutic level of 5-15 ng/ml. Tacrolimus is changed to oral dosing when tolerated and can be tapered off after day +90 if no GvHD is present. Methotrexate 5 mg/m^2 will be administered intravenously on days 1, 3, 6 and 11 post transplant. Day 11 methotrexate may be held if the patient has symptomatic mucositis.

Study Enrollment:

The study population for this research will consist of participants from:

Only at MDACC

Estimated Accrual:

Total Accrual at MDACC: 250

Estimated monthly accrual at MDACC: 7

Accrual Comments:

Up to 250 patients will take part in this study. All will be enrolled at M. D. Anderson. We estimate that an average of 7 patients will be enrolled each month, based on our prior experience.

Is this an NCI-Cancer Therapy Evaluation Protocol (CTEP)? No

Is this an NCI-Division of Cancer Prevention Protocol (DCP)? No

Statistical Considerations:

Treatments and Outcomes. This is phase III clinical trial of allogeneic stem cell transplantation for AML/MDS patients, having age between 3 and 70 years, who are either in complete remission or not in CR (NCR). All patients will be randomized between two preparative regimens. Both regimens have been studied in recent MDACC trials and found to be adequately safe and effective, warrenting this randomized comparison. The first preparative regimen (FluBu) consists of fludarabine (dose = 40 mg/m2) + intravenous (IV) busulfan using a subgroup-specific PK targeted dose (target dose = 6000 micromolar x minute in patients up to age 60 with ECOG performance status 0 or 1 or 4000 for patients 61-70 years of age or performance status 2). The second preparative regimen (FluCloBu) consists of fludarabine (dose = 10 mg/m2) + clofarabine (dose = 30 mg/m2)+ IV busulfan dosed in the same manner. The primary endpoint will be T = progression-free survival (PFS) time, defined as the time from date of transplant to death from any cause or disease progression. Secondary endpoints will include overall survival (OS) time, and the indicator G100 that the patient has grade 3 or 4 acute graft-versus-host disease at any time during the first 100 days post transplant,

Design and Trial Conduct. 250 patients will be entered. The two preparative regimens, FB and FCB, will be compared in terms of PFS time using a group sequential design(38) with two-sided O'Brien-Fleming boundaries, with up to two interim tests and one final test, having overall Type I error .05 and power .90

to detect an improvement of Pr(T > 12 months) from a null value of .56 to a target value of .71, equivalently, to detect a change in median PFS from 14.35 to 25.29 months. The null value of Pr(T > 12 months) was determined by assuming that Pr(T > 12 months | CR) = .65 and Pr(T > 12 months | NCR) = .50, based on experience with Flu + IV Busulfan, and the assumption that Pr(CR) = .40, giving null Pr(T > 12 months) = .40x.65 + .60x.50 = .56. The decision boundaries, in terms of the standardized log rank statistic, are +/- 3.7103, +/- 2.5114, +/- 1.993 to be applied when, respectively, 52.16, 104.31, and 156.46 events (death or progression) have been observed in both arms combined. The Pocock-Simon method will be used to dynamically balance the randomization on the binary (CR, NCR) indicator, using the Department of Biostatistics Clinical Trial Conduct website.

Data Analyses. Kaplan-Meier plots will be used to estimate the unadjusted OS and PFS time distributions. Time-to-event regression analyses will be used to evaluate the ability of treatment arm and patient covariates to predict OS and PFS, with the model underlying model chosen based on preliminary goodness-of-fit analyses of the data. The rate of 100 day severe GvHD will be estimated by tabulations and computation of posterior credible intervals, overall and within the CR and NCR. To account for the treatment anand baseline covariates, Pr(GvHD within 100 days) will be estimated using logistic regression.

Data Safety Monitoring Board / DSMB at MDACC:

Select the name of the data safety monitoring board (DSMB) monitoring this protocol:
MDACC DSMB

Protocol Monitoring:

Does this protocol have a schedule for interim and final analysis? Yes

Provide a summary or schedule of interim analysis.
The two preparative regimens, Flu-Bu and Flu-Clo-Bu, will be compared in terms of PFS time using a group sequential design(38) with two-sided O'Brien-Fleming boundaries, with up to two interim tests and one final test, having overall Type I error .05 and power .90 to detect an improvement of Pr(T > 12 months) from a null value of .56 to a target value of .71, equivalently, to detect a change in median PFS from 14.35 to 25.29 months.

Protocol Monitoring Plan:

Toxicities will be scored according to CTCAE version 3 criteria. The study will be monitored by the department of SCT&CT at our regular protocol outcome meetings.

Intellectual Property:

1. Does this study include any agents, devices, or radioactive compound (or drug) manufactured at MD Anderson Cancer Center or by a contract manufacturer? No

Investigational New Drugs (IND):

Does this protocol require an IND? No

☒Please confirm that the protocol meets all criteria for exemption according to 21CFR 312.2(b) **noted below:**

(b) Exemptions. (1) The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of this part if all the following apply:

(i) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;

(ii) If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;

(iii) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

(iv) The investigation is conducted in compliance with the requirements for institutional review set forth in part 56 and with the requirements for informed consent set forth in part 50; and

(v) The investigation is conducted in compliance with the requirements of 312.7.

[redacted]

Rationale for Exemption:
Please include a detailed rationale as to why this drug should be considered exempt from FDA IND regulations, including any available references to the prior use of the regimen or drug combination in human subjects.

Optimize the dose of busulfan used with stem cell transplantation for AML/MDS; Patients have received fixed dose of 130 mg/m^2 in prior studies with an median AUC of 5000 microMol-min and most AUCs ranging from approximately 3500-7500 microMol-min. There was no increase in toxicity seen within this range. In this study we will us PK adjusted dosing to target a busulfan AUC of 6000 microMol-min hoping to improve control of leukemia without excess toxicity.

If this protocol includes an FDA Approved Therapy, please list the disease, dose and route of administration:

	Approved Use	Proposed in this Protocol
Disease:	Busulfan-CML	Preparative Regimen for BMT
Dose:	0.8 mg/kg q6 hrs for 16 doses with cyclophosphamide	Once Daily dose for 4 days - PK adjusted to a systemic exposure of AUC 6,000
Route of Administration:	IV	IV

Investigational Device (IDE):

Does this study utilize an Investigational Device? No

Sponsorship and Support Information:

Does the Study have a Sponsor, Supporter or Granting Agency? Yes

Sponsor Name: Sanofi

Support Type: Industry Funding
Agent Name(s): Clofarabine

This Sponsor/Supporter/Granting Agency will receive data.

Regulatory Requirements

Radioactive Material:

Does this study involve the administration of radioisotopes or a radioisotope labeled agent?	No

Biosafety:

Does this study involve the use of Recombinant DNA Technology? No

Does this study involve the use of organisms that are infectious to humans? No

Does this study involve human/animal tissue other than blood derived hematopoietic stem cells? N/A

Questions should be addressed to the Transfusion Medicine Tissue Coordinator at 713-792-8630.

Laboratory Tests:

Is there any biomarker testing in this study being used to determine patient/participant eligibility, treatment assignment, or management of patient/participant care?

- ( ) Yes
- (•) No
- ( ) Not Applicable For This Protocol

Manufacturing:

Will you manufacture in full or in part (split manufacturing) a drug or biological product at the M. D. Anderson Cancer Center for the proposed clinical study? No

Student/Trainee Information:

Is this research being conducted as a partial fulfillment for completion of a degree? No