THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Abstract Page

Phase II Study of Timed Sequential Busulfan in Combination with Fludarabine in Allogeneic Stem Cell Transplantation
2011-0958

Core Protocol Information

Short Title:	Allogeneic Transplantation Using Timed Sequential Busulfan and Fludarabine Conditioning
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Full Title:	Phase II Study of Timed Sequential Busulfan in Combination with Fludarabine in Allogeneic Stem Cell Transplantation
Protocol Phase:	Phase II
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Version:	23
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Abstract

Objectives:

Primary Objective:
This is a Phase II study which primary objective is to assess the day 100 non-relapse mortality rates of timed sequential busulfan and fludarabine conditioning regimen.

Secondary Objectives:
To evaluate efficacy of this therapy by studying the following endpoints:
a. Overall Survival,
b. Progression free survival,
c. Neutrophil and Platelet engraftment, and
d. Estimate acute and chronic GVHD.

Tertiary Objectives:
To study impact of timed sequential busulfan therapy on:
a. Gene expression in tumor cells, and
b. Cytokines (both in plasma and cells).
c. The change in busulfan pharmacokinetics (PKs) between day -13 and day -6 dosing.

Rationale: (Be as concise as possible)

Timed sequential chemotherapy (TST)- delivery of a second course of chemotherapy 8-10 days after the previous one - was developed to enhance antitumor effect. Very promising efficacy was seen in clinical studies conducted to date. In vitro studies showed enhanced leukemia cell kill by recruiting a higher proportion of non cycling leukemic cells in to cell cycle after first course of chemo making them more susceptible to the second course of chemotherapy. Subsequent early clinical studies in patients with AML were promising and documented enhanced antileukemic activity. Forty percent of patients with acute myeloid leukemia achieved long-term remission in these initial studies at Johns Hopkins. German AML group noted 68% complete remission (CR) rate in refractory patients and 84% remission rate as frontline therapy in a phase II study, leading to ongoing phase III study. French AML group likewise showed 61% CR rate in refractory patients, which led to a phase III study comparing this approach to standard therapy. While overall results were not significantly different, relapse rate was significantly lower in younger patients receiving TST compared with those receiving standard therapy, 36% vs. 50%. Children's cancer group noted most impressive results in a phase III study enrolling 589 AML subjects. Patients were randomized to receive second course of therapy 6 days(TST) after the first one or at the standard interval of 14 – 28 days depending on bone marrow results. Event free survival was 42% in TST group and 27% in the standard group (p=0.0005) and overall survival was 52% and 42% in two groups respectively (p=0.04). This principle was further tested in a multicenter German phase II study in patients with refractory AML. In this study patients received a course of induction chemotherapy 4 days before reduced intensity conditioning allogeneic transplantation. Event free survival was 37% in these refractory patients, which is quite notable because expected EFS in this group of patients would be 15% - 20%.

We would like to apply these principles in our current study to treat patients with high-risk hematological malignancies. We would like to split busulfan in the conditioning regimen in two phases given 6 days apart. In the first phase we will give busulfan 80mg/m2 for two days. We will do PK analysis with first dose and adjust the dose of phase II busulfan to achieve a target AUC of 20,000 µmol/L over whole course of treatment. Effectively patients will receive the same dose as our standard but will receive a third or less of busulfan in first phase and about 2/3 in second phase 6 days later. This will also enable us to define optimal dose of busulfan with this schedule of drug administration. We will also do correlative studies on blood samples obtained at set time point to study the cytokine profile, which was postulated in invitro studies to cause increased anti tumor efficacy of this approach. A second correlative study will be to look at gene expression analysis of tumor cells at different time points to see if pretherapy at day 13 has any impact on gene expression.

Eligibility: (List All Criteria)

Inclusion:

1) Patients with high-risk hematologic malignancies with anticipated poor prognosis with non transplant therapy, including those in remission or with induction failure and after treated or untreated relapse. Diagnoses to be included a) Acute myeloid leukemia; b) Acute lymphocytic leukemia; c) Chronic myeloid leukemia; d) Chronic lymphocytic leukemia; e) Myelodysplastic syndrome; f) Myeloproliferative syndromes; g) Non-Hodgkins lymphoma; h) Hodgkins Lymphoma; i) Multiple myeloma.
2) Patients must have a histocompatible stem cell donor. An HLA-identical related donor or an 8/8 matched unrelated donor.
3) Age 5 to 75 years old.
4) Performance score of >/= 70 by Karnofsky/Lansky or PS 0 to 1 (ECOG </=1).
5) Left ventricular ejection fraction at least 40%.
6) Adequate pulmonary function with FEV1, FVC and DLCO >/=50% of expected corrected for hemoglobin and/or volume. Children unable to perform pulmonary function tests (e.g., less than 7 years old) pulse oximetry of >/= 92% on room air
7) Creatinine clearance (calculated creatinine clearance is permitted) should be >40 ml/min.
8) Bilirubin </= 2 x the upper limit of normal (except Gilbert's Syndrome). SGPT (ALT) < 200.
9) 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.
10) Patient or patient's legal representative, parent(s) or guardian able to sign informed consent.

Exclusion:

1) HIV seropositivity.
2) Uncontrolled infections.

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

Studies that exclude children must have appropriate justification. Please select all that apply:

Other:
Please Specify:
This is an investigator-initiated study and there is no Phase I study for pediatric patients.

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:

Leukemia, Myeloproliferative Diseases

Treatment Agents/Devices/Interventions:

Busulfan, Fludarabine, Stem Cell Transplantation

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. The allogeneic blood stem cell collection is a standard procedure for which a separate consent will be signed. Donors (related or unrelated) must meet standard medical eligibility criteria for allogeneic blood stem cell donation.

Preparative Regimen.
Acetaminophen should not be used between D-14 (starting 24 hours before the test dose of IV Bu) and D0, since there is a major interference between these drugs and the metabolism of Bu which is likely to contribute in a major way to cause serious liver damage.

Busulfan first two doses.
The first two doses of Busulfan, 80 mg/m^2 can be administered as an outpatient or as an inpatient. The first Busulfan dose will be based on actual body weight and will be given IV over three hours by controlled-rate infusion pump.

Pharmacokinetic-guided (PK-guided) treatment**:**
The first two doses of Busulfan of 80 mg/m2 will be administered on day -13 and -12, it will be will be given IV by controlled-rate infusion pump. PK studies will be done with the first dose. The pharmacokinetic- guided daily high-dose busulfan dose(s) will be started immediately upon completion of the daily fludarabine on days -6 to -3. The busulfan doses will be diluted in normal saline and administered IV daily by controlled rate infusion pump starting immediately after the completion of Fludarabine.

Busulfan is administered at the dose calculated to achieve a **total** (including first two doses delivered on day -13 and -12) systemic exposure of 20,000 ± 12% µMol-min based on the pharmacokinetic studies. (PK studies may also be done on day -6 if the physician deems it necessary for patient safety or in order to adjust the final two days of Busulfan on day -4 and day -3 to meet this total systemic exposure.) We will also analyze the percentage of patients who achieve the targeted systemic exposure (± 10%) based on first dose PK guided recommendation and characterize the variability and change between the two busulfan PKs in the patient population.

D-6 to D-3 Fludarabine administration.
Fludarabine will be dosed per actual body weight/actual body surface area. No arbitrary dose adjustment(s) based on a perceived need for using adjusted body weight/body surface area will be allowed for Fludarabine.

Fludarabine is administered at the dose of 40 mg/m2 in 100 ml of NS IV on each of four (4) consecutive days by a controlled-rate pump.

Stem Cell infusion.
Fresh or cryopreserved bone marrow or peripheral blood progenitor cells will be infused on day 0. Depending on arrival time, patients who receive a graft from an unrelated donor might have one day delayed from D0.

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.

G-CSF administered at a dose of 5 mcg/kg/day (rounded up the nearest vial size) subcutaneously beginning on D+7, and continuing until the absolute neutrophil count (ANC) is > 500 x 10/L for 3 consecutive days.

Antiseizure prophylaxis will include either phenytoin or levetiracetam as follows (choice of medication is at the discretion of the PI or attending physician).

For phenytoin dose: 600 mg PO for first dose, then 300 mg or 600 mg daily thereafter depending on BSA (if BSA is less than 1.8m2, dose is 300 mg).
1. First dose (600 mg) is given the evening prior to first 80 mg/m2 dose of busulfan (day -14) and the evening prior to first therapeutic dose of busulfan (day -7, day of admission).
2. Dose (according to BSA) on day -13, day -12, day -6, day -5, day -4 and day -3 is given 30 to 60 minutes prior to busulfan dose.
3. Dose (according to BSA) on day -11 and day -2 is given approximately 24 hours after the last busulfan dose from the day prior.
4. Phenytoin (or fosphenytoin) may be used IV in patients unable to swallow oral formulation.
5. Phenytoin levels are not routinely checked.

Levetiracetam: Dose is 500 mg per dose
1. First dose (500 mg) is given the evening prior to first 80 mg/m2 dose of busulfan (day -14) and the evening prior to first therapeutic dose of busulfan (day -7, day of admission).
2. Dose on day -13, day -12, day -6, day -5, day -4 and day -3 is given as 500 mg twice daily PO or IV (first dose of the day should be timed 30 to 60 minutes before busulfan).
3. Dose on day -11 and day -2 is 500 mg PO or IV BID, with last dose being approximately 24 hours after the last dose of busulfan from the day prior.

Other supportive care (allopurinol, menstrual suppression, prophylactic antibiotics, empiric antibiotics, IVIG, transfusions of blood products, hyperalimentation, etc.) as indicated.

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

Only at MDACC

Estimated Accrual:

Total Accrual at MDACC: 200
Estimated monthly accrual at MDACC: 3

Accrual Comments:
The expected accrual rate is 3 patients per month.

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

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

Statistical Considerations:

Overview

The original study design was a randomized Phase II study of two separate timed sequential Busulfan/fludarabine conditioning regiments with 50 patients in each arm. The primary objective was to the compare the Day 100 non-relapse mortality (NRM) rate between the arms. On March 4, 2014, the MDACC Data and Safety Monitoring Board (DSMB) met and approved the study team's request to stop the randomization for this study and continue the study as a single-arm study with increased accrual onto the higher dose arm. The total accrual was almost complete at that time, and there were no significant differences in NRM between the arms and virtually no chance of seeing a difference at the end of the trial (predictive probability =0.0003). Therefore, we present below the revised statistical considerations for this study halting the randomization and continuing the study with an increase of 100 additional patients (150 patients total) in the higher dose arm.

The revised primary objective will be to assess the NRM rate in the higher dose arm. Secondary objectives include assessing overall and progression-free survival, time to platelet and neutrophil engraftment, the cumulative incidence of acute and chronic GVHD, and correlative studies of cytokines at serial time points.

Safety Monitoring
We will use Bayesian monitoring rules to monitor the 100-day NRM rate in the high dose arm and stop the study if there is strong evidence at any time that this rate exceeds 10%. We choose 10% rather than 20% based on the low NRM rate found in the randomized portion of the trial. Formally, we will stop accrual to the high dose arm if at any time:

$$\Pr(\text{Day 100 NRM in high dose arm} > 0.10 \mid \text{Data}) > 0.98$$

We assume a Beta (0.2, 1.8) prior distribution for the probability of NRM corresponding to a 10% mean, and assume a constant rate of 0.10 for the standard of care. Stopping boundaries and operating characteristics were generated using the Department of Biostatistics' Multc Lean Desktop version V2.1.

Patients will be monitored in cohorts of size 10. The stopping boundaries for this rule are:

# Total Patients in high dose arm (cohorts of 10)	Stop the trial if there are this many or more NRM100 total in the high dose arm:
10	4-10
20	6-20
30	8-30
40	9-40
50	11-50
60	12-60
70	13-70
80	15-80
90	16-90
100	17-100
110	19-110
120	20-120
130	21-130
140	23-140
150	Always stop with 150 patients in high dose arm

The operating characteristics of this rule are presented below. There is approximately a 6% chance of stopping the study early if the true Day 100 NRM rate in the high dose arm is 10%.

True NRM rate in high dose arm	Pr(early stop)	Sample Size (25th, 50th, 75th percentiles)		
0.05	0.0014	150	150	150
0.10	0.0634	150	150	150
0.20	0.5172	60	130	150
0.30	0.9302	30	50	80
0.40	1.0000	10	20	30

Analysis Methods
Continuous data will be summarized using descriptive statistics (mean, standard deviation, median, inter-quartile range, range). Categorical data will be summarized using frequency counts and percentages.

The proportion of patients with NRM will be reported for each treatment arm, along with 95% Bayesian credible intervals. A sample size of 150 patients in the high dose arm will provide a confidence interval of (5.2%, 14.8%) for a 10% Day 100 NRM rate.

Overall survival and progression-free survival will be calculated from the time of transplant by the method of Kaplan and Meier. Cox proportional hazards regression analysis will be used to assess the association between these survival parameters and clinical and treatment covariates of interest.

The time to platelet and neutrophil engraftment will be calculated from the time of transplant and estimated by the Kaplan-Meier method. The cumulative incidence of acute and chronic GVHD with the competing risk of relapse will be estimated using the method of Gooley and the method of Fine and Gray will be used to model this incidence by disease and clinical characteristics of interest. Secondary analysis will also include analyzing NRM with these methods while taking into account the competing risk of deaths due to other causes within 100 days. Generalized linear mixed models will be used to assess the association between cytokines over time and treatment and other factors.

The change in busulfan PK between the first dose (day -13) and the third dose (day -6) will be compared using t test. Percentage of patients who achieve the targeted systemic busulfan exposure (±10%) based on first dose PK recommendation and overall population PK will be summarized using descriptive statistics. The PK analysis will be correlated with toxicity and efficacy.

Descriptive statistics will be used to summarize adverse events by treatment arm. The number (%) of subjects with treatment emergent adverse events will be reported. Frequency counts and percentages will also be presented of subjects with serious adverse events, adverse events leading to withdrawal.

All other safety parameters will be summarized using descriptive statistics or frequency counts. Graphical summaries will be used where appropriate.

Data Safety Monitoring Board / DSMB at MDACC:

Select the name of the data safety monitoring board (DSMB) monitoring this protocol:
Not Applicable

Please explain:
This study is not randomized nor blinded.

Protocol Monitoring:

Does this protocol have a schedule for interim and final analysis? No

Provide a rationale for no interim analysis.

We will use Bayesian monitoring rules to monitor the 100-day NRM rate in the high dose arm and stop the study if there is strong evidence at any time that this rate exceeds 10%. We choose 10% rather than 20% based on the low NRM rate found in the randomized portion of the trial. Formally, we will stop accrual to the high dose arm if at any time:

$$\Pr(\text{Day 100 NRM in high dose arm} > 0.10 \mid \text{Data}) > 0.98$$

Protocol Monitoring Plan:

Patient registration will be done in CORE. Monitoring will be performed by the MD Anderson Clinical Research Support Center according to institutional policies.

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.

In this study, we plan to optimize the dose and schedule of busulfan used with stem cell transplantation. 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 20,000 µMol-min based on the pharmacokinetic studies but change the schedule, hoping to improve control of hematologic malignancies without excess toxicity. At our institution, we have treated and published on more than 400 patients receiving busulfan and fludarabine conditioning pretransplant.

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	80 mg/m2 daily doses (days -13, -12), then 4 daily PK-adjusted doses (days -6 to -3) with fludarabine 40 mg/m2
Route of Administration:	IV	IV

Investigational Device (IDE):

Does this study utilize an Investigational Device? N/A

Sponsorship and Support Information:

Does the Study have a Sponsor, Supporter or Granting Agency? No

Regulatory Requirements

Radioactive Material:

Does this study involve the administration of radioisotopes or a radioisotope labeled agent?	N/A

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