Gemcitabine/Clofarabine/Busulfan and Allogeneic Transplantation for Aggressive Lymphomas

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Protocol Body

1.0 Background

1.0 Primary:

1. To define the maximum tolerated dose (MTD) of infusional gemcitabine combined with fixed doses of clofarabine and busulfan in patients with lymphoma receiving an allogeneic stem-cell transplant (alloSCT).
2. To estimate the day +100 success rate, defined as percentage of patients who are alive, engrafted and without grade 3-4 graft-vs.-host-disease (GVHD).

1.1 Secondary:

1. To estimate the day +100 success rate [defined as percentage of patients who are alive, engrafted and without grade 3-4 graft-vs.-host-disease (GVHD)]
2. To estimate the rate of event-free (EFS)
3. To estimate the rate of overall survival (OS)
4. To estimate the response rate (RR) [defined as # of responses / # of patients with measurable tumors]
5. To estimate the complete reponse (CR) rate [defined as # of complete responses / # of patients with measurable tumors]
6. To estimate the incidence of grade 2-4 and grade 3-4 acute GVHD
7. To estimate the incidence of limited and extensive chronic GVHD.

2.0 Background

Stem-cell transplantation is standard treatment for patients with relapsed Hodgkin's or non-Hodgkin's lymphoma.[1,2] However, results of autologous stem-cell transplantation are poor for patients who fail to respond to salvage chemotherapy.[3,4] Such patients are usually considered for an allogeneic stem-cell transplant (alloSCT) if they have an available matched sibling donor (MSD) or matched unrelated donor (MUD). An allogeneic SCT offers the advantages of graft-vs.-lymphoma (GVL) effect as well as infusion of a tumor-free apheresis product. In addition, reduced intensity combinations have substantially increased the safety and tolerability of alloSCT. Unfortunately, aggressive lymphomas often progress shortly after an alloSCT due to rapid tumor cell growth outpacing GVL.[5-7] Thus, development of novel regimens that are both safe and effective against aggressive lymphomas is a major unmet need.

2.1 Nucleoside analogue/busulfan studies for transplantation.

Nucleoside analogues (NA) and alkylators are synergistic based on inhibition of DNA damage repair.[9] Exploiting their synergy we have conducted successful studies of busulfan combined with fludarabine for acute myeloblastic leukemia[9,10] or with clofarabine[11] for acute lymphoblastic leukemia as conditioning regimens for alloSCT. In the autologous transplant setting we have developed a regimen of

gemcitabine/busulfan/melphalan (GemBuMel) with high activity against poor-prognosis relapsed lymphomas.[12] The side effect profile of this regimen, including mucositis and rash, was safe and manageable in the autologous transplant setting, but was found to be excessively toxic for use in alloSCT.

Preclinical studies of our collaborators Valdez and Andersson have shown increased synergy resulting from combinations of double nucleoside analogues (gemcitabine and clofarabine) added to busulfan in several chemotherapy-refractory lymphoma cell lines (Daudi, J45.01 and U937).[13] The experiments indicate increased DNA damage response through the ATM-CHK2 and ATM-CHK1 pathways, leading to cell cycle checkpoint activation and apoptosis.

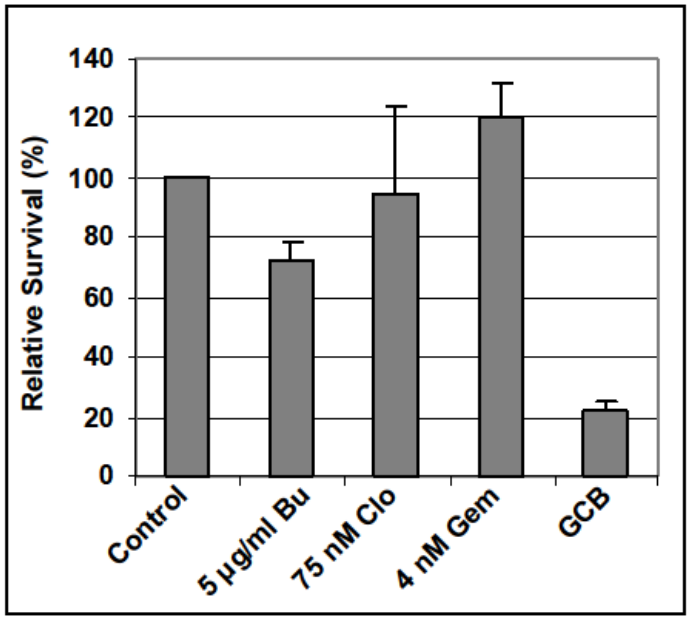

Figure 1. Cytotoxicity of Busulfan and nucleoside analogs (gemcitabine and clofarabine) toward Daudi B-cell lymphoma cells. Cells were continuously exposed to drugs alone, or in combination, for 96 hours and analyzed by MTT assay. Bu or B, busulfan; Clo or C, clofarabine; Gem or G, gemcitabine

Based on the results of these experiments we decided to study clinically gemcitabine/clofarabine/busulfan in patients with relapsed aggressive lymphomas receiving an alloSCT. We hypothesize that this regimen will be safe in this setting for the following reasons:

1) Omission of melphalan should result in less mucositis than GemBuMel, which is desirable in the alloSCT setting, 2) CloBu is immunosuppressive enough to ensure engraftment[11-14], and 3) CloBu results in less graft-vs.-host disease (GVHD) than BuMel.[11]

3.0 Patient Eligibility

3.1 Inclusion Criteria:

1. Age 12 to 65 years of age.
2. Patients with refractory B-cell or T-cell non-Hodgkin's lymphoma or Hodgkin's lymphoma who are eligible for allogeneic transplantation.
3. An 8/8 HLA matched (high resolution typing at A, B, C, DRB1) sibling or unrelated donor.
4. Left ventricular EF >/= 45%.
5. FEV1, FVC and corrected DLCO >/= 50%.
6. Adequate renal function, as defined by estimated serum creatinine clearance >/=50 ml/min (using the Cockroft-Gault formula: creatinine clearance = [(140-age)*kg/(72*serum creatinine)] * 0.85 if female) and/or serum creatinine </=1.6 mg/dL.
7. Serum bilirubin </= 2x upper limit of normal.
8. SGPT </= 2x upper limit of normal.
9. Able to sign informed consent.
10. Men and women of reproductive potential must agree to follow accepted birth control methods for the duration of the study. Female subject is either post-menopausal or surgically sterilized or willing to use an acceptable method of birth control (i.e., a hormonal contraceptive, intra-uterine device, diaphragm with spermicide, condom with spermicide, or abstinence) for the duration of the study. Male subject agrees to use an acceptable method for contraception for the duration of the study.

3.2. Exclusion Criteria:

1. Patient with active CNS disease.
2. Pregnancy (positive Beta HCG test in a woman with child bearing potential defined as not post-menopausal for 12 months or no previous surgical sterilization) or currently breast-feeding. Pregnancy testing is not required for post-menopausal or surgically sterilized women.
3. Active hepatitis B, either active carrier (HBsAg +) or viremic (HBV DNA >/=10,000 copies/mL, or >/= 2,000 IU/mL).
4. Evidence of either cirrhosis or stage 3-4 liver fibrosis in patients with chronic hepatitis C or positive hepatitis C serology.
5. HIV infection.
6. Active uncontrolled bacterial, viral or fungal infections.
7. Exposure to other investigational drugs within 2 weeks before enrollment.
8. Grade >/= 3 non-hematologic toxicity from previous therapy that has not resolved to </= grade 1.
9. Radiation therapy to head and neck (excluding eyes), and internal organs of chest, abdomen or pelvis in the month prior to enrollment.
10. Prior whole brain irradiation.
11. Prior autologous SCT in the prior 3 months.

4.0 Pretreatment evaluation

The following will be performed about 30 days prior to start treatment.

4.1. Complete history and physical examination.
4.2. Baseline evaluations to include CXR, chemistry panel, hematology survey. Bone marrow biopsy with aspirate for morphology, immunophenotyping, cytogenetic analysis, and FISH when indicated.
4.3. Serum immunoglobulins, beta-2 microglobulin will be checked in the peripheral blood.
4.4. CT and/or PET-CT of the neck, chest, abdomen and pelvis for lymphoma staging.

5.0 Treatment Plan

The transplant day is referred to as day zero (D0), treatment plan activities prior or after D0 are denominated as day minus (D-) or day plus (D+).

Preparative Regimen:

Between D-15 and D-8 Busulfan test dose.

Busulfan test dose can be administrated in the outpatient setting prior to admission for the first therapeutic Busulfan dose or given in the inpatient setting on D-8. The Busulfan test dose of 32 mg/m^2 will be based on actual body weight and will be given IV over 60 minutes by
controlled-rate infusion pump.

D-9 or -7 Hospital Admission.

Admission is on D-7 for outpatient test dose and on D-9 for inpatient test dose. Patients should be preferentially admitted on Sunday, or Monday for pharmacokinetic directed therapy.

D-6 and D-4 Gemcitabine Administration.

As in our prior trial of GemBuMel (2006-0803) and all other currently active gemcitabine trials (2010-0142 and 2010-0506), this drug will be administered as a 75 loading mg/m^2/dose IV targeting the desired steady state concentration of 20 µmolar. This will be immediately followed by an infusion at a fixed rate of 10 mg/m^2 /min over varying lengths of time per study cohort. Each gemcitabine dose will be immediately followed by clofarabine, which will be in turn immediately followed by busulfan. Gemcitabine dose will be based on adjusted body weight for patients > 20% above ideal body weight.

Table 1. Gemcitabine Dose Escalation Levels

Cohort	Daily Gemcitabine dose (d-6 and d-4) (*)	Total Gemcitabine dose (mg/m2)	Clofarabine (mg/m2/day)	Busulfan target AUC/day (mg/m2/day)
1	40 min infusion (475 mg/m^2)	950	40	4,000 (100 mg/m^2)
2	60 min infusion (675 mg/m^2)	1350	40	4,000 (100 mg/m^2)
3	90 min infusion (975 mg/m^2)	1950	40	4,000 (100 mg/m^2)
4	120 min infusion (1275 mg/m^2)	2550	40	4,000 (100 mg/m^2)
5	150 min infusion (1575 mg/m^2)	3150	40	4,000 (100 mg/m^2)
6	180 min infusion (1875 mg/m^2)	3550	40	4,000 (100 mg/m^2)

* Each Gem infusion is preceded by 75 mg/m^2 Gemcitabine given as a one min bolus dose.

D-6 to D-3 Clofarabine administration.

Clofarabine will be administered at a dose of 40 mg/m^2 diluted in NS to produce a final concentration of 0.4mg/mL, and infused over one hour on each of four consecutive days (days -6 through -3). On days -6 and -4 clofarabine will immediately follow the infusion of gemcitabine. Clofarabine will be dosed per actual body weight/actual body surface area.

D-6 to D-3 Busulfan administration. Pharmacokinetic-guided (PK-guided) treatment:
The PK-guided daily high-dose busulfan doses will be started immediately upon completion of
the daily clofarabine doses. The busulfan doses will be diluted in normal saline and administered over 3 hours daily by controlled rate infusion pump.

Busulfan will be administered at the dose calculated to achieve a systemic exposure dose of 4000 µMol-min in normal saline over three hours IV every twenty-four hours for four consecutive days (days -6 to -3), starting immediately after the completion of clofarabine, between 5 and 6:30 AM.

Fixed dose busulfan: If it is not feasible to perform pharmacokinetic monitoring, patients will receive a fixed busulfan dose of 100 mg/m^2/day for 4 days, which is expected to yield a median daily AUC of 4,000 µMol.min-1. Busulfan dose will be based on adjusted body weight for
patients > 20% above ideal body weight.

Acetaminophen must not be used between days -9 and 0. Other drugs known to interfere with the metabolism of busulfan should not to be concomitantly used during the chemotherapy administration up to and including the day of transplantation, including voriconazole, itraconazole, metronidazole, and tyrosine kinase inhibitors. These drugs should be stopped at least one week prior to start of busulfan as feasible.

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

Patients receiving a graft from a matched 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. The Thymoglobulin will be administered as per regular departmental routines, and will be infused in the afternoon of respective days so not to interfere with the chemotherapy administration.

D-14 and D-7 and then on D+1 and D+8 Rituximab only for patients with CD20+ tumors.

Patients with CD20+ disease will receive rituximab IV at 375 mg/m^2 (based on actual body weight) on D-14 and D-7 and then on Day +1 and D+8. Rituximab infusion will follow SCT&CT department standard practice.

D0 Stem Cell infusion:

Fresh or cryopreserved bone marrow or peripheral blood progenitor cells will be infused on day 0. 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.

Filgrastim-sndz (G-CSF, Zarxio) administered at a dose of 5 mcg/kg/day (rounded up the nearest vial size) subcutaneously.

GVHD prophylaxis will include Tacrolimus and mycophenolate mofetil (MMF) 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 per departmental standards. MMF will start at 1,000 mg IV TID on day 0 after cell infusion and will be changed to oral dosing (1:1 conversion) when tolerated. MMF will be discontinued without tapering on day +60.

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

* A biosimilar of rituximab may be used.6.0 Evaluation During Study

6.1. Assessment of DNA damage analysis:

This correlative study will be optional for patients participating in this trial. DNA damage will be assessed by quantitative analysis of the phosphorylation of histone 2 AX (gamma-H2AX) using flow cytometry. Samples (20 mL of blood) will be drawn in 2 heparinized tubes. The first sample (baseline) will be collected prior to the busulfan test dose. Samples 2 and 3 will be drawn a day after the first and second dose of gemcitabine, respectively. The gamma-H2AX assay will be conducted in the laboratory of Drs. Valdez and Andersson.[15] Briefly, mononuclear cells will be isolated and immunostained with a monoclonal antibody specific to gamma-H2AX and an anti-mouse IgG antibody conjugated to Alexa Fluor 488. Fluorescence of at least 10,000 cells will be determined by flow cytometry.

6.2. To be performed around engraftment time:

1. Chimerism studies from peripheral blood performed on separated T-cells and myeloid cells.
2. Physical examination and adverse event documentation including GvHD assessment.

6.3. To be performed at approximately 3, 6 and 12 months post transplant.

These evaluations follow our standard practice and are done to monitor engraftment and disease status. If clinically indicated these studies may be done at other time points which can replace the nearest planned timepoint.

1. Chimerism studies from peripheral blood performed on separated T-cells and myeloid cells.
2. At each visit, physical examination and adverse event documentation including GvHD assessment.
3. Disease specific assessment with bone marrow aspirate with cytogenetics, minimal residual disease using flow panel for CLL, serum immunoglobulins in peripheral blood and CT and/or PET-CT for lymphoma staging as indicated.

6.4. After the first year patients will be followed up for disease status, presence of GVHD and survival as per routine follow-up and standard of practice for patients receiving allogeneic stem cell transplantation.

The following lab tests are to be performed as frequently as clinically indicated:CBC, differential, platelets, SGPT, calcium, glucose, uric acid, magnesium, serum bilirubin, BUN and creatinine, serum protein, albumin, alkaline phosphatase, electrolytes, urinalysis, tacrolimus levels and CMV antigenemia.

7.0 Definitions

Active treatment administration is defined from the first day of treatment administration as outlined in the treatment plan through D0.

Active treatment period is defined from the first day of treatment administration through Day
+30.

Follow-up period is defined from BMT Day +31 until five years of treatment completion.

Engraftment is defined as the evidence of donor derived cells (more than 95%) by chimerism studies in the presence of neutrophil recovery by day 28 post stem cell infusion.

Neutrophil recovery is defined as a sustained absolute neutrophil count (ANC) > 0.5 x 10^9/L for 3 consecutive days.

Engraftment date is the first day of three (3) consecutive days that the ANC exceeds 0.5×10^9/L.

Delayed engraftment is defined as the evidence of engraftment beyond day 28 post hematopoietic stem cell (HSC) infusion achieved after the administration of therapeutic (high dose) hematopoietic growth factors.

Primary Graft failure is defined as failure to achieve an ANC > 0.5×10^9/L for 3 consecutive days by day 28 post HSC infusion, with no evidence of donor-derived cells by bone marrow chimerism studies in the absence of persistent or recurring disease.

Secondary graft failure is defined as a sustained decline of ANC <0.5×10^9/L for 3 consecutive days after initial documented engraftment with no evidence of disease progression.

Autologous reconstitution is defined by the presence of ANC > 0.5×10^9/L without evidence of donor-derived cells by bone marrow chimerism studies. This can occur at initial engraftment or later after initial engraftment has been documented.

8.0 Off Study Criteria

1. Patient may be removed from study if in the judgment of the Principal Investigator further treatment is not in the best interest of the patient.
2. Unacceptable pattern of toxicity.
3. Patient withdraws informed consent.
4. Inability or unwillingness to have follow-up visits and/or laboratory tests required by this protocol.
5. After five years after treatment completion.
6. Patients who experience graft failure or disease progression will continue on study for survival only.

9.0 Adverse Effect Assessment

Assessment of the Adverse Events Severity.

The severity of the adverse events (AEs) will be graded according to the Common Terminology Criteria v3.0 (CTCAE).
Events not included in the CTCAE chart will be scored as follows:

General grading:

Grade 1: Mild: discomfort present with no disruption of daily activity, no

treatment required beyond prophylaxis.
Grade 2: Moderate: discomfort present with some disruption of daily activity, require treatment.
Grade 3: Severe: discomfort that interrupts normal daily activity, not responding to first line treatment.
Grade 4: Life threatening: discomfort that represents immediate risk of death

Grading for specific syndromes:

Veno-occlusive disease (VOD):

Grade 3: Bili >2mg/dl with at least two of the following: increased weight >4% from baseline, ascites or hepatomegaly
Grade 4: pulmonary and or renal failure

Pulmonary events not caused by CHF (interstitial pneumonitis (IP), pulmonary hemorrhage (DAH):
Grade 1: CXR showing mild infiltrates or interstitial changes Grade 2: mild SOB
Grade 3: requires supplemental oxygen, or is a documented infection Grade 4: requires intubation

Transplant related microangiopathy:

Grade 1: No treatment required
Grade 2:Requires steroids and/or plasma transfusions Grade 3: Requires plasma exchange

Cytokine storm or engraftment syndrome:

Grade 1: No treatment required
Grade 2: Treatment required
Grade 3: Organ dysfunction
Grade 4: Total Bilirubin >5

Hemorrhagic Cystitis:

Grade 1: minimal or microscopic bleeding/pain
Grade 2: gross bleeding/pain and spasms
Grade 3:

transfusion/irrigation
required
Grade 4: dialysis required

Causality Assessment.

For the purpose of this study the treatment plan (preparative regimen followed by allogeneic stem cell transplantation) is defined as the “transplant package”; therefore adverse events known to be caused by components of the transplant package and its direct consequences will be scored as definitive related. Adverse events known to be related to drugs used for the treatment of GVHD and Infection episodes will be scored as probable related. When the relationship of the adverse event cannot be ruled out with certainty the AE may be considered possible related. Adverse events known to be related to drugs used for supportive treatment will be scored as unrelated.

The principal investigator will be the final arbiter in determining the casualty assessment.
List of most common expected adverse events.

1. Infections in the presence or absence of neutropenia: fungal, bacterial and or viral infections.
2. Fever: Non-neutropenic or neutropenic without infection
3. Acute graft versus host disease (aGVHD): most commonly manifested by skin rash, diarrhea and abnormal liver function tests could also present with some degree of fever, upper gastrointestinal symptoms (nausea and vomiting) mucositis and eye dryness.
4. Gastrointestinal (GI tract): the GI tract manifestations could be not only due to direct damage from the preparative regiment but also be a manifestation of GVHD or infections. Therefore, the time course and its presentation are crucial when assessing these as adverse events. Nausea/vomiting, mucositis, diarrhea when presented within first 7 to 10 days most likely will be related to the preparative regimen.
5. Skin rash: not related to GVHD could be caused by chemotherapy used for the preparative regimen or antibiotics used a supportive treatment.
6. Transaminitis: liver function test elevation.
7. Pulmonary events: not related to CHF most likely caused by drug injury or infection. These could present with a pneumonitis pattern manifested with shortness of breath, pulmonary infiltrates on chest radiograph, sometimes accompanied by fever and cough and progress to acute respiratory insufficiency and a diffuse bilateral alveolar pattern.
8. Cytokine Storm/ engraftment syndrome: most likely caused by released cytokines.
9. Hemorrhagic cystitis: not related to chemotherapy agents used in the proposed preparative regimen is most likely caused by viral infection.
10. Thrombotic thrombocytopenic purpura (TTP).

11. Veno-occlusive Disease of the Liver (VOD): could be caused by busulfan. Some antimicrobial agents have been also incriminated in its development.

12. Fluid overload due to hydration required for conditioning regimen, blood product transfusions and or IV alimentation.

13. Graft failure.

14. Chronic GVHD.

15. For the purpose of this study the following events would not be considered adverse events and would not be recorded in the database:

    1. Flu-like symptoms not associated with infection
    2. Abnormal laboratory findings considered associated to the original disease
    3. Isolated changes in laboratory parameters such as electrolyte, magnesium and metabolic imbalances, uric acid changes, elevations of ALT, AST, LDH and alkaline phosphatase.

Adverse events considered serious.

Adverse events data collection.

From the start of preparative regimen up to D+100 the collection of adverse events will reflect the onset and resolution date and maximum grade; beyond this point some events considered related to chronic GVHD or late complications post transplant might be recorded only with the first date of their awareness with no grade or resolution date.

Intermittent events should be labeled as such and followed until resolution. If a patient is taken off study while an event is still ongoing, this will be followed until resolution unless another therapy is initiated. Pre-existing medical conditions will be recorded only if an exacerbation occurs during the active treatment period. Co-morbid events will not be scored separately.

As stated in the treatment plan, patients treated on this protocol will required supportive care treatment (concurrent medication). These medications are considered standard of care and have no scientific contributions to the protocol, therefore no data will be captured on the various medications needed or their side effects.

AE and Protocol Deviations Reporting Requirements.

Adverse events will be reported accordingly to MDACC (HSRM chapter 15.001) policy and procedures. This study will be conducted in compliance however in the event of any protocol deviations or violations these will be reported accordingly to MDACC (HSRM chapter 25).

10.0 Definition of Dose-Limiting Toxicity (DLT)

For both stage 1 and stage 2 of the trial, dose limiting toxicity (DLT) is defined as any of the following events occurring within 30 days from transplant:

1. Grade 3-4 mucositis lasting for more than 3 days at peak severity.
2. Grade 3-4 skin toxicity lasting for more than 3 days at peak severity.
3. Grade 4 nonhematological noninfectious toxicity.

Enrollment will continue to proceed following the adaptive design as determined by the Continual Reassessment Method (CRM). CRM will assign a dose level (e.g., dose X) to up to 2 new patients (e.g., patient A and B). If, based on medical considerations, subsequent patients (e.g., patients C, D...) have to initiate treatment before the toxicities of patients A or B have been assessed, these subsequent patients will be treated at the next lower dose level, dose X-1.

DLT will be assessed for each patient on day 30. A maximum of six subsequent patients can be enrolled at level X-1 before toxicities of patients A and B are assessed.

11.0 Statistical Considerations

Regimen and dose levels.

This is a phase I/II trial of intravenous busulfan and clofarabine given over days -6 to -3, and gemcitabine given on days -6 and -4, as a preparative regimen for patients with aggressive lymphoma undergoing allogeneic stem cell transplantation. The doses of busulfan and clofarabine (each given in days -6, -5, -4, -3) will be fixed, and the primary scientific goal in Phase I is to determine the best dose of gemcitabine among the six levels 475, 675, 975, 1275, 1575, 1875 mg/m2/day, Hereafter, these will be referred to as dose levels 1, 2, 3, 4, 5, 6.

Phase I.
The primary scientific goal in Phase I is to determine an optimal gemcitabine dose (d*). The Bayesian Time to Event Continual Reassessment Method (TiTE-CRM,[16, 17]) will be applied to determine d* in phase I. DLT will be defined as grade 3-4 mucositis lasting for more than 3 days at peak severity, grade 3-4 skin toxicity lasting for more than 3 days at peak severity, occurring within 30 days from transplant, or grade 4 nonhematological noninfectious toxicity.

Patient outcome will be the time of occurrence of DLT or, if DLT has not yet occurred by day 30, the outcome will be the patient's follow-up time without DLT. Denoting the time of follow up or DLT by T, and the right-censoring indicator C=1 if T is a follow up time without DLT and C=0 if T is the time of observed DLT, each patient's data will consist of the pair (T,C), with T no longer than 30 days. A patient's outcome (T,C) will be considered "fully evaluated" if either C= 0 (DLT has occurred at some

time up to day 30) or (T,C) = (30,1), which says that no DLT has occurred by day 30. The TiTE-CRM will be applied with target DLT probability .20, cohort size 2, and maximum sample size 30 patients, and an estimated accrual rate of 1 patient per month. Operating characteristics of the TiTE-CRM design are summarized in the following Table 1. Values are based on 2,000 simulations of the trial under each scenario. The computations were carried out using the subroutine "titecrm" of the R program, "dfcrm," provided by Y-K Cheung., which is freely available from the website http://www.columbia.edu/~yc632/ under *An R package for phase I clinical trials*.

Table 1. Operating characteristics of TiTE CRM Dose-Finding Design.

		Dose level					
		1	**2**	**3**	**4**	**5**	**6**
	Gemcitabine Dose, mg/m2/day	475	675	975	1275	1575	1875
Scenario							
1	True Prob(Tox)	0.1	0.2	0.3	0.4	0.5	0.6
	% Selected	21.6%	52.4%	22.6%	3.1%	0.4%	0%
	Average N Patients Treated	9.1	11.0	6.3	2.3	0.9	0.4
	Average N Patients w/Tox	0.9	2.2	1.8	0.9	0.4	0.3
2	True Prob(Tox)	0.3	0.4	0.5	0.6	0.7	0.8
	% Selected	95.6%	4.2%	0.2%	0%	0%	0%
	Average N Patients Treated	24.4	3.5	1.3	0.5	0.2	0.1
	Average N Patients w/Tox	7.3	1.4	0.6	0.3	0.1	0.05
3	True Prob(Tox)	0.2	0.4	0.6	0.7	0.8	0.9
	% Selected	90.0%	10%	0.1%	0%	0%	0%
	Average N Patients Treated	23.1	4.9	1.2	0.5	0.2	0.04
	Average N Patients w/Tox	4.6	2.0	0.7	0.3	0.2	0.03
4	True Prob(Tox)	0.05	0.1	0.15	0.2	0.25	0.3

	% Selected	1.0%	11.2%	27.4%	30.0%	20.9%	9.5%
	Average N Patients Treated	2.9	5.3	7.0	6.2	4.8	3.8
	Average N Patients w/Tox	0.1	0.5	1.1	1.2	1.2	1.1
5	True Prob(Tox)	0.02	0.06	0.1	0.14	0.17	0.2
	Selected	0%	1.9%	11.6%	23.2%	30.2%	32.9%
	Average N Patients Treated	1.8	3.0	4.6	6.0	6.5	8.2
	Average N Patients w/Tox	0.04	0.2	0.5	0.8	1.2	1.8

Safety Monitoring Rule for Both Phase I and Phase II Based on TRM100 Rate

The event TRM100 is defined to be either (1) transplant-related mortality or (2) grade 4 regimen-related extramedullary non-infectious toxicity occurring within 100 days posttransplant. Note that DLT and TRM100 are not disjoint events, in that any TRM100 event occurring prior to day 30 is also dose limiting.

The following safety rule to control TRM100 rate will be applied. This rule will be applied both (i) in phase I to control the risk of TRM 100 at all doses that have been explored by the TiTE-CRM based on 30-day toxicity, and (ii) in phase II to control the risk of TRM100 at the MTD chosen in phase I, for the subset of patients treated at any given dose level, “d,” and in phase II, for all patients treated at the MTD chosen in phase I.

1. For application in phase I, “dose d” below in the rule means any given Gemcitabine dose that has been used by the TiTE-CRM. If a dose d is found to have unacceptably high TRM100 rate in phase I, then neither dose d nor any higher doses may be used to treat any future patients in phase I or phase II, and furthermore this rule overrides the TiTE-CRM.
2. For application in phase II, the rule will be applied to the dose, d*, previously chosen in as “optimal” phase I and used to treat patients in phase II. If a dose d* is found to have unacceptably high TRM100 rate in phase II, then neither dose d* nor any higher doses may be used to treat any future patients. If this occurs, then d* will be replaced by the dose one level lower (d*-1), and phase II will be re-started at d*-1. In that case, all patients treated at d*-1 in phase I will be counted toward the maximum of 50 patients treated at d*-1. The same TRM100 safety rule will then be applied, with d*-1 in place of d*. If d*-1 is found to have unacceptably high TRM100 rate, the trial will be terminated.

The Safety Rule. In addition to the primary endpoint of DLT within 30 days, another safety monitoring rule based on TRM100 will be implemented using the method of Thall and Sung. Any given dose level d will be considered to have an unacceptably high TRM100, and will

be stopped if the probability of TRM100 being higher than 20% is greater than 95%. Formally, denoting the probability of TRM100 at dose d by q(d), assuming that q(d) follows a beta(.20, .80) prior, the dose d and all higher doses will be discontinued due to excessively high TRM100 if Pr{ q(d) > .20 } data} > .95. To compute the properties of this rule using the program "multc99," a beta(200,800) prior was assumed for a "standard" probability, qS. Based on application of this rule to up to 50 patients at d, this implies that d has unacceptable TRM100 if [# TRM100 observed at dose d] / [# evaluated by day 100 at dose d] is greater than or equal to 2/2, 4/6, 5/9, 6/12, 7/16, 8/19, 9/23, 10/26, 11/30, 12/34, 13/38, 14/42, or 15/49. The operating characteristics of this TRM100 monitoring rule are summarized in Table 2a, assuming a maximum of 25 patients, and in Table 2b, assuming a maximum of 50 patients.

Table 2a. Operating characteristics of the TRM100 monitoring rule, rule in phase I, based on 10,000 simulations per case assuming a maximum of 25 patients at any given dose level.

		Sample Size Quartiles		
True Pr(TRM100)	**Probability of Stopping Early**	**25th**	**50th (Median)**	**75th**
.10	0.02	25	25	25
.20	0.16	25	25	25
.30	0.48	8	25	25
.40	0.80	5	10	21
.50	0.97	2	5	10

Table 2b. Operating characteristics of the TRM100 monitoring rule in phase II, rule based on 10,000 simulations per case assuming a maximum of 50 patients at any given dose level.

		Sample Size Quartiles		
True Pr(TRM100)	**Probability of Stopping Early**	**25th**	**50th (Median)**	**75th**
.10	0.02	50	50	50
.20	0.19	50	50	50
.30	0.68	8	27	50
.40	0.96	5	10	36
.50	0.999	4	5	18

Phase II.
The primary scientific goal in Phase II is to estimate the day +100 success rate [defined as percentage of patients who are alive, engrafted and without grade 3-4 graft-vs.-host-disease (GVHD)], rate of event-free (EFS), overall survival (OS), response rate (RR), complete response (CR) rate, incidence of grade 2-4 and grade 3-4 acute GVHD, and incidence of limited and extensive chronic GVHD. A maximum of 50 patients will be treated in phase II. Phase II will be conducted using the optimal dose (d*), chosen in phase I. All patients treated at d* in phase I will be counted as part of the initial phase II sample.

Response rate (RR) = # of responses / # of patients with measurable tumors

Complete response (CR) rate = # of complete responses / # of patients with measurable

tumors

Phase II Rule for Monitoring DLT. Since ptox(d*) cannot be determined with perfect reliability in phase I, to guard against the possibility of excessive DLT, DLT will also be monitored in phase II. The probability of DLT at the selected dose d* from phase I will be considered too high if Pr{ptox(d*) > .20 | phase II data} > .80, with this rule applied after each cohort of 10 patients in the phase II sample. This rule implies that d* is too toxic if [# DLTs]/[# patients evaluated] is greater than or equal to 5/10, 8/20, 11/30, or 13/40. If this occurs, then d* will be replaced by the dose one level lower (d*-1), and phase II will be re-started at d*-1. In that case, all patients treated at d*-1 in phase I will be counted toward the maximum of 50 patients treated at d*-1. The same safety rule will then be applied, with d*-1 in place of d*. If d*-1 is found to be too toxic, the trial will be terminated.

Table 3. Operating characteristics of the phase II safety rule for DLT.

True Prob(DLT)	Pr(de-escalate or stop)	Sample Size Quartiles
.10	.002	50 50 50
.20	.08	50 50 50
.30	.48	20 50 50
.40	.90	10 20 30

Data Analysis.
The counts and percentages of each type of toxicity, GVHD by grade, and GF will be tabulated overall and by gemcitabine dose. EFS and OS time distributions will be estimated using the method of Kaplan and Meier.[19]

12.0 Background Drug Information

12.1 Busulfan (IV Busulfex®)

Therapeutic Classification: Antineoplastic Alkylating agent
Pharmaceutical data: Busulfan injection is a sterile, pyrogen-free solution provided in a mixture of dimethylacetamide (DMA) and polyethyleneglycol 400 (PEG400). It is supplied in 10 ml single use ampoules at a concentration of six (6) mg busulfan per ml. Each ampoule contains 60 mg of busulfan in 3.3 ml of DMA and 6.7 ml of PEG400. When diluted in normal saline or D5W to a concentration of 0.5 mg/ml, the resulting solution must be administered within eight hours of preparation.

Stability and storage: Ampoules should be stored refrigerated at 2-8°C (35-46°F). Stable at 4°C for at least twelve months. DO NOT use if the solution is cloudy or if particulates are present.
Solution Preparation: Prepare the busulfan solution as follows: mix into normal saline to a final concentration of 0.5 mg/mL.
In each bag 6.0 mg busulfan (1.0 ml at 6 mg/ml and 11 ml saline) should be added to compensate for drug lost in the tubing with each infusion (approximately 12 ml at 0.5 mg/ml is lost in the tubing when using the controlled rate infusion pump).
Route of Administration: It is to be noted, that a sufficient amount of diluted busulfan should be added to compensate for the amount needed to prime the IV tubing; when hanging the infusate, the tubing should be primed with the busulfan solution and connected as close to the patient as possible, i.e. by a 3-way connector at the level of the

central venous catheter. After completed infusion, the tubing with remaining busulfan (approximately 12 mL) should be disconnected and discarded. All busulfan infusions should be performed by programmable pump.
CAUTION: DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.
An infusion pump will be used with the busulfan solutions as prepared above. A new infusion set must be used for administration of each dose. Prior to and following each infusion, flush the catheter line with normal saline or (approximately 5 ml). Start the infusion at the calculated flow rate. DO NOT infuse concomitantly with another intravenous solution of unknown compatibility. If a delay in administration occurs after the infusion solution is prepared, the properly identified container should be kept at room temperature (20-25°C), but administration must be completed within eight hours of preparation including the three hour drug infusion.

Side effects: Dose limiting toxicity is expected to be hematological when used without stem cell support. Other toxicities seen frequently following high-dose busulfan in preparative regimens for bone marrow transplantation include: veno-occlusive disease (VOD), nausea, vomiting, pulmonary fibrosis, seizures, rash, and an Addison's-like syndrome.
Mechanism of action: Interferes with DNA replication and transcription of RNA through DNA alkylation, and ultimately results in the disruption of nucleic acid function.
Animal Tumor Data: Busulfan has been shown to be active against a variety of animal neoplasm in vivo, including mouse sarcoma 180 and Ehrlich's mouse ascites tumor.
Human Pharmacology: Limited pharmacology data are available for the parenteral formulation to be used in this study and is detailed in the evaluation of IV Bu in a Phase II Trial using IV Bu at 0.8 mg/kg BW given over 2 hr every 6 hr for a total of 16 doses and when administered once daily for 4 days at a dose of 130 mg/m2 in combination with Fludarabine. The pharmacokinetic data suggests that the plasma decay of the formulation fits an open one-compartment model with linear pharmacokinetics in the dose range of 12 mg-130 mg/m2. Based on studies of oral Bu, the drug is reported to be extensively metabolized; twelve metabolites have been isolated, but most have not been identified. The drug is slowly excreted in the urine, chiefly as methanesulfonic acid. Ten to fifty percent (10-50%) of a dose is excreted as metabolites within twenty-four (24) hours.

12.2 Clofarabine (Clolar®)

Clofarabine is formulated as a concentration of 1mg/mL in United States Pharamacopeia (USP) sodium chloride (9mg/mL), and USP water for injection (qs to 1mL). Clofarabine is supplied in 2 vial sizes: a 10mL flint vial and 20mL flint vial. The 10 mL flint vials contain 5mL (5mg) of solution and the 20mL flint vials contain 20mL (20mg). For both vial types, the pH range of the solution is 4.0 to 7.0. The solution is clear with color ranging from colorless to yellow and is free from visible particulate matter.
Expected toxicities: myelosuppression, nausea/vomiting, diarrhea, mucositis, skin rash (particularly hand-foot syndrome), fatigue, mental status changes/coma, allergic reactions (including fever, muscle aches, edema, dyspnea), congestive heart failure, conjunctivitis, anorexia, febrile neutropenia, pruritus, headache, flushing and pyrexia, liver failure.
Clofarabine Formulation and Stability: Clofarabine vials containing undiluted clofarabine for injection should be stored at 25°C or 77°F with temperature excursion permitted to 15 to 30°C or 59 to 86°F. Ongoing self-life stability indicate that clofarabine is stable for 36 months at 25°C (±2°C) and 60% (±5%) relative humidity and for 6 months at 40°C

(±2°C) and 75% (±5%) relative humidity.

12.3 Rituximab (Rituxan®)
Description: Rituximab is a monoclonal antibody targeted against CD20 primarily found on B lymphocytes. Rituximab causes cell lysis through complement mediated cytotoxicity and antibody-dependent cytotoxicity. A biosimilar of rituximab may be used.

Preparation and stability: Dilute with NS or D5W to a final concentration of 1-4mg/mL. Solution is stable at 2-8 degrees C for 24 hours and additional 24 hours at room temperature. Rituximab is supplied as 100mg and 500mg vials.

Administration: Administer according to institutional standards.

Adverse reactions: infusion reactions (fever, chills, hypotension), rarely anaphylaxis, acute respiratory distress syndrome, arrhythmias, lymphopenia, infection, hepatitis B reactivation, rarely progressive multifocal leukoencephalopathy, skin rash, tumor lysis syndrome, nausea/vomiting, arthralgias, myalgias, and severe mucocutaneous reactions (including Stevens-Johnson Syndrome and toxic epidermal necrolysis).

Storage: Diluted solutions of Rituximab should be stored refrigerated at 2-8 degrees C. Rituximab vials should be stored at 2-8 degrees C. and protected from direct sunlight. Do not freeze or shake.

See package insert for additional information.

12.4. Thymoglobulin (Thymoglobulin®)
Thymoglobulin® (Rabbit antithymocyte globulin, Genzyme Corporation) will be used as an in vivo immunosuppression.
Therapeutic classification: Polyclonal anti-lymphocyte preparation.
Stability and storage requirements: The lyophilized powder should be stored in a refrigerator at 2 to 8°C (36 to 46°F). Thymoglobulin should be used within 4 hours after reconstitution if kept at room temperature. For vials containing the unreconstituted lyophilized powder, the product is stable for 36 months at 5-3°C and 12 months at 37°C. Reconstituted product is stable for 72 hours at room temperature 20 to 25°C.
Preparation: Immediately before intravenous administration, dilute reconstituted Thymoglobulin in isotonic saline or dextrose solution to a total infusion volume of 50 to 500 mL (usually 50 mL of IV admixture solution per 25 mg vial).
Usual dosage range: 4.5-7.5 mg/kg over 3 days.
Administration: The recommended route of administration is intravenous infusion through an
in-line 0.22 micron filter into a high-flow vein. Thymoglobulin should be infused over a minimum of 6 hours for the first infusion and over at least 4 hours on subsequent days of therapy.
Known side effects and toxicities: The most common adverse reactions are fever, chills, leukopenia, thrombocytopenia, rashes, systemic infections, abnormal renal function tests, and serum sickness-like symptoms. Other reported side effects are arthralgia, chest and/or back pain, diarrhea, dyspnea/apnea, nausea and vomiting.
Mechanism of action: Possible mechanisms by which Thymoglobulin may induce immunosuppression *in vivo* include: T-cell clearance from the circulation and modulation of T-cell activation, homing, and cytotoxic activities. Thymoglobulin is thought to induce T-cell depletion and modulation by a variety of methods, including Fc receptor-mediated

complement-dependent lysis, opsonization and phagocytosis by macrophages, and immunomodulation leading to long term depletion via antibody dependent cell-mediated cytotoxicity and activation induced cell death, commonly referred to as apoptosis.

12.5. Gemcitabine (Gemzar®)
SYNONYM(S): Gemcitabine hydrochloride, difluorodeoxycytidine, 2',2'-difluorodeoxycytidine, dFdC, LY 188011.
CLASSIFICATION: Antimetabolite, cytotoxic
MECHANISM OF ACTION:
Gemcitabine, a pyrimidine analog, is structurally similar to cytarabine, but has a wider spectrum of antitumour activity due to its different cellular pharmacology and mechanism of action.
Gemcitabine is metabolized intracellularly to two active metabolites, Gemcitabine diphosphate (dFdCDP) and Gemcitabine triphosphate (dFdCTP). The cytotoxic effects of Gemcitabine are exerted through incorporation of dFdCTP into DNA with the assistance of dFdCDP, resulting in inhibition of DNA synthesis and induction of apoptosis. Gemcitabine is a radiation-sensitizing agent.5 It is cell-cycle phase specific (S and G1/S-phases).
PHARMACOKINETICS: 3- to 4-fold interpatient and intrapatient variability. widely distributed into tissues; also present in ascitic fluid. plasma protein binding< 10%. Metabolized intracellularly by nucleoside kinases to active metabolites dFdCDP and dFdCTP; also metabolized intracellularly and extracellularly by cytidine deaminase to inactive metabolite difluorodeoxyuridine (dFdU). active metabolite(s)dFdCDP, dFdCTP. inactive metabolite(s)dFdU. Urine92-98% over one week (89% as dFdU, < 10% as Gemcitabine) after a single dose of 1000 mg/m2 given over 30 minutes. Urine92-98% over one week (89% as dFdU, < 10% as Gemcitabine) after a single dose of 1000 mg/m2 given over 30 minutes. terminal half life IV infusion < 70 min: 0.7-1.6 h. IV infusion 70-285 min: 4.1-10.6 h

SPECIAL PRECAUTIONS:

Carcinogenicity: No information found.

Mutagenicity: Not mutagenic in Ames test but mutagenic in mammalian *in vitro* mutation test. Gemcitabine is clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.

Fertility: Decreased spermatogenesis and fertility in male mice.

Pregnancy: FDA Pregnancy Category D. There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

Breastfeeding is not recommended due to the potential secretion into breast milk

SIDE EFFECTS: Allergic reaction (4%, severe 0.2%), Leucopenia (62%, severe 9%), *neutropenia* (63%, severe 25%) nadir 7-10 days, recovery within 7 days, th*rombocytopenia*
(24%, severe 5%) nadir 7-10 days, recovery within 7 days, cardiac arrhythmia (2%, severe
0.2%), edema/peripheral edema (28%, severe 3%), hemolytic uremic syndrome (0.3%), asthenia (42%, severe 2%), asthenia (42%, severe 2%), fever (37%, severe < 1%), alopecia
(14%), skin rash (25%, severe < 1%), constipation (8%, severe < 1%), diarrhea (12%,

severe
< 1%), *emetogenic potential:* low moderate, nausea and vomiting (64%, severe 18%), stomatitis (8%, severe < 1%), hematuria (31%, severe < 1%), elevated alkaline phosphatase
(55%, severe 9%), elevated AST (67%, severe 9%), elevated ALT (68%, severe 10%), elevated bilirubin (13%, severe 2%), infection (9%, severe 1%), decreased level of consciousness (9%, severe < 1%), peripheral neuropathy (3%), dyspnea (8%, severe 1%),
dyspnea (8%, severe 1%), elevated BUN (16%, severe 0%), elevated creatinine (7%, severe
< 1%), Proteinuria (36%, severe < 1%), flu-like symptoms (19%, severe 1%)
Hemolytic uremic syndrome has been infrequently reported and is characterized by microangiopathic hemolytic anemia, thrombocytopenia and renal failure. The syndrome can present either acutely with severe hemolysis, thrombocytopenia and rapidly progressive renal failure, or more insidiously with mild or no thrombocytopenia and slowly progressive renal failure. The etiology of hemolytic uremic syndrome is unknown.The onset of the syndrome has been reported to occur during and shortly after Gemcitabine therapy. If not treated promptly, the syndrome may result in irreversible renal failure requiring dialysis. Therefore, patients with impaired renal function should be monitored closely while being treated with Gemcitabine.

Elevated liver enzymes: Gemcitabine causes transient and reversible elevations of liver function enzymes in about two-thirds of patients. However, these increases are rarely of clinical significance and there is no evidence of increasing hepatic toxicity with either longer duration of Gemcitabine treatment or cumulative dose.

Fever/Flu-like symptoms: Fever of any severity was reported in 37% of patients. It is frequently associated with other flu-like symptoms such as headache, chills, cough, rhinitis, myalgia, fatigue, sweating and insomnia. These symptoms are usually mild and transient, and rarely dose-limiting. The use of acetaminophen may provide symptomatic relief.

Severe pulmonary toxicity: Acute dyspnea may sometimes occur with Gemcitabine therapy, but is usually self-limiting. However, severe pulmonary toxicities such as pulmonary edema, interstitial pneumonitis and adult respiratory distress syndrome have rarely been reported. The symptoms are manifested as progressive dyspnea, tachypnea, hypoxemia and pulmonary infiltrates on chest radiograph that are sometimes accompanied by fever and cough. Pulmonary toxicities usually occur after several cycles of Gemcitabine, but have also been seen as early as the first cycle. Risk factors for pulmonary toxicities include prior radiation to the mediastinum.
Because of its structural similarities to cytarabine, Gemcitabine is thought to cause lung injury by the same mechanism by inducing pulmonary capillary leakage. Management of pulmonary toxicities consists of discontinuation of Gemcitabine and early supportive care with bronchodilators, corticosteroids, diuretics, and/or oxygen. Although pulmonary toxicities may be reversible with treatment, fatal recurrence of severe pulmonary symptoms was reported in one patient upon rechallenge with Gemcitabine.

Skin rash**:** Typically mild to moderate in severity, with macular or finely granular maculopapular pruritic eruption on the trunk and extremities. It is not dose-limiting and usually responds to topical corticosteroids. If needed, antihistamines such as diphenhydramine can be used.

SOLUTION PREPARATION AND COMPATIBILITY:

Injection: 200 mg and 1000 mg vials (as the hydrochloride salt). Store at room temperature.

Reconstitute 200 mg vial with 5 mL of NS without preservative and 1000 mg vial with 25 mL of NS without preservative to yield a Gemcitabine concentration of 38 mg/mL. Reconstitution of concentrations greater than 40 mg/mL may result in incomplete dissolution and should be avoided. Reconstituted solution is stable for 24 hours at room temperature and should not be days at room temperature and under refrigeration. However, the manufacturer recommends that the admixture be used within 24 hours since the solution does not contain preservatives.

13.0 References

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