THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Abstract Page

High-dose gemcitabine, busulfan and melphalan with hematopoietic cell support for patients with relapsed/refractory Hodgkin's disease. 2010-0142

Core Protocol Information

Study Chairman:	Yago Nieto
Department:	Stem Cell Transplantation and Cellular Therapy
Phone:	713-792-8750
Unit:	423
Full Title:	High-dose gemcitabine, busulfan and melphalan with hematopoietic cell support for patients with relapsed/refractory Hodgkin's disease.
Protocol Phase:	Phase II
Version Status:	Terminated 12/14/2018
Version:	15
Document Status:	Final

Abstract

Objectives:

Primary Endpoint

1. To determine the event-free survival (EFS) of patients with poor prognosis relapsed or refractory Hodgkin's disease (HD) after high-dose chemotherapy (HDC) with Gemcitabine/Busulfan/Melphalan (GemBuMel).

Secondary endpoints

1. To determine the overall survival (OS) of these patients.
2. To describe the toxicity profile of this treatment.
3. To analyze the effect of single nucleotide polymorphisms (SNPs) of gemcitabine metabolic genes on patient toxicity and outcome.

Rationale: (Be as concise as possible)

High-dose chemotherapy (HDC) with autologous stem-cell transplant (ASCT) is standard treatment of patients with relapsed Hodgkin's disease (HD) or primary induction failure. Numerous prognostic analyses, including our own, have identified independent adverse prognostic factors for outcome after HDC: length of prior disease-free interval, active or

residual tumor at the time of HDC (particularly as determined by PET), extranodal disease, relapse within a prior radiation field, and number of salvage lines of chemotherapy.

Since its start in January 2007, we have enrolled in 2006-0803, 119 patients with refractory lymphoid tumors receiving an autologous transplant (78 with HD, 34 non-Hodgkin's lymphoma, and 7 with myeloma). Gemcitabine was administered as a loading dose of 75 mg/m2, calculated to reach a Css of 15 micromolar, followed by a continuous infusion at 10 mg/m2/min. We found that the daily x 6 and the every other day (3 doses) schedules of gemcitabine were associated with excessive skin toxicity. In contrast, we did not observe significant skin toxicity in the 2-dose schedule of gemcitabine. In this 2-dose schedule gemcitabine is administered on the first treatment day of busulfan (day -8) and melphalan (day -3) (Table 1). The optimal length of infusion of gemcitabine was established at 4.5 hours following its loading dose, on each of its two treatment days.

Table 1. GemBuMel schedule

	-8	-7	-6	-5	-4	-3	-2	-1	0
Gemcitabine (loading dose of 75 mg/m^2 followed by 4.5 hour CI at 10 mg/m^2/min)	X					X			
Busulfan (target AUC of 4,000 AUC microM.min/day)	X	X	X	X					
Melphalan 60 mg/m^2/day						X	X		
PBPC infusion									X

At its optimal dose level for future testing, GemBuMel produced in this phase I study a reversible side-effect profile of mucositis (60% grade 2, 13% grade 3), skin toxicity (13% grade 2) and self-limited elevation of the transaminases (21% grade 2, 7% grade 3) among 25 patients treated to date at this level. There were no grade 4 or 5 toxicities.

The regimen had high level of activity across all diagnoses. Specifically, among patients with HD, the EFS and OS rates of pts with HD are 76% and 98%, respectively, with a current median follow-up of 8.5 (range 1-36) months. We compared these results with those of a contemporaneous cohort of refractory HD patients (N=25) treated at our department since January 2007 with BEAM. These patients met eligibility criteria for 2006-0803 but received BEAM off protocol for various reasons. Both cohorts have been followed for a similar length of time: GemBuMel, 8 (1-37) months, and BEAM, 13 (1-33) months. The group treated with GemBuMel presented significantly better EFS (76% vs. 36%, P=0.004) and OS rates (97% vs. 65%, P=0.04) than those treated with BEAM. These superior results were observed despite there being more patients with poor prognostic features in the GemBuMel than in the BEAM cohorts. In view of these highly encouraging results we wish to study GemBuMel further for patients with refractory HD. We will exclude from eligibility patients younger than 12 and older than 70, as we have

no experience with this regimen in these age groups.

Eligibility: (List All Criteria)

Inclusion:

1) Age 12 to 70 years

2) Patients with relapsed Hodgkin's disease and one or more of the following: 1) Less than complete response to first-line chemotherapy, 2) Relapse within 12 months of completion of first-line chemotherapy, 3) Relapse within a prior irradiation field, 4) Less than complete metabolic response to second-line chemotherapy, 5) Second relapse or beyond, 6) Extranodal disease at the time of relapse, 7) Presence of B symptoms at the time of persistent disease upon completion of first-line chemotherapy, or of relapse, progressive disease, 8) Bulky disease (defined as any lesion greater than 5 cm) at the time of persistent disease upon completion of first-line chemotherapy, or of relapse, progressive disease.

3) 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 </=1.8 mg/dL.

4) Adequate hepatic function, as defined by SGOT and/or SGPT </=3 x upper limit of normal; serum bilirubin and alkaline phosphatase </=2 x upper limit of normal, unless due to disease involvement

5) Adequate pulmonary function with FEV1, FVC and DLCO >/=50% of expected corrected for hemoglobin and/or volumen.

6) Adequate cardiac function with left ventricular ejection fraction >/=40%. No uncontrolled arrhythmias or symptomatic cardiac disease.

7) Zubrod performance status <2.

8) Negative Beta HCG text in a woman with child-bearing potential, defined as not post-menopausal for 12 months or no previous surgical sterilization

Exclusion:

1) Patients with grade >/= 3 non-hematologic toxicity from previous therapy that has not resolved to </= grade 1.

2) Patients with prior whole brain irradiation

3) Patients with 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) Active infection requiring parenteral antibiotics.

6) HIV infection, unless the patient is receiving effective antiretroviral therapy with undetectable viral load and normal CD4 counts

7) Patients having received radiation therapy to head and neck (excluding eyes), and internal organs of chest, abdomen or pelvis in the month prior to enrollment.

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

Please provide a letter from the Sponsor stating if a Phase I study planned for patients <18 years of age. (May include file attachment)

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:

Lymphoma

Treatment Agents/Devices/Interventions:

Busulfan, Gemcitabine, Melphalan

Proposed Treatment/Study Plan:

Is treatment assignment randomized? ○ Yes ● No

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

Outpatient PKs

Day	Date	Treatment
	_____	Busulfan 32mg/m^2 test dose with PKs (outpatient)
-12	_____	Palifermin 60 micrograms/kg (outpatient) Do not start on **Monday/Tuesday/Wednesday**
-11	_____	Palifermin 60 micrograms/kg (outpatient)
-10	_____	Palifermin 60 micrograms/kg (outpatient)
-9	_____	Admit
-8	_____	Gemcitabine 2775 mg/m^2 IV (75 mg/m^2 bolus followed by 2700 mg/m^2) / Busulfan AUC 4,000 (with PKs)

-7	_____	Busulfan AUC 4,000
-6	_____	Busulfan AUC 4,000
-5	_____	Busulfan AUC 4,000
-4	_____	Rest
-3	_____	Gemcitabine 2775 mg/m^2 IV (75 mg/m^2 bolus followed by 2700 mg/m^2) / Melphalan 60 mg/m^2 IV
-2	_____	Melphalan 60 mg/m^2 IV
-1	_____	Rest
-0	_____	**Stem Cell Transplant** / Palifermin 60 micrograms/kg IV
+1	_____	Palifermin 60 micrograms/kg IV
+2	_____	Palifermin 60 micrograms/kg IV

Inpatient PKs

Day	Date	Treatment
-13	_____	Palifermin 60 micrograms/kg (outpatient) **Start on Friday or Saturday**
-12	_____	Palifermin 60 micrograms/kg (outpatient)
-11	_____	Palifermin 60 micrograms/kg (outpatient) / Admit
-10	_____	Busulfan 32mg/m^2 test dose
-9	_____	Rest
-8	_____	Gemcitabine 2775 mg/m^2 IV (75 mg/m^2 bolus followed by 2700 mg/m^2) / Busulfan AUC 4,000
-7	_____	Busulfan AUC 4,000
-6	_____	Busulfan AUC 4,000
-5	_____	Busulfan AUC 4,000
-4	_____	Rest

-3	_____	Gemcitabine 2775 mg/m^2 IV (75 mg/m^2 bolus followed by 2700 mg/m^2) / Melphalan 60 mg/m^2 IV
-2	_____	Melphalan 60 mg/m^2 IV
-1	_____	Rest
-0	_____	**Stem Cell Transplant** / Palifermin 60 micrograms/kg IV
+1	_____	Palifermin 60 micrograms/kg IV
+2	_____	Palifermin 60 micrograms/kg IV

Caphosol oral rinse, 30 mL 4 times a day, starting on day -9
Glutamine mouthwashes, 15 g 4 times a day, starting on day -9.
Dexamethasone 8 mg IV BID from day -9 PM to day -2 PM
G-CSF according to BMT standard routine
Piridoxine will be started at 100 mg IV/PO on day -1.

Patients with positive CD20+ tumors by immunohistochemistry will receive rituximab 375 mg/m2 on days +1 and +8 per its usual schedule when combined with high-dose chemotherapy.

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

Only at MDACC

Estimated Accrual:

Total Accrual at MDACC:	80
Estimated monthly accrual at MDACC:	3

Accrual Comments:
Up to 80 patients will take part in this study. All will be enrolled at M. D. Anderson. We estimate that an average of 3 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:

Outcome and Model

This is a Phase II clinical trial in Hodgkin's disease patients with high risk of relapse. The maximum total sample size will be 80 patients, with an accrual rate of 4 patients per month. The patient population will include PET- and PET+ patients.

The primary objective of the study is EFS. It is hypothesized that the combined treatment GBM will prolong the median EFS from 15.8 months to 38.6 months, comparing with the standard treatment

BEAM. This corresponds to a 2-year EFS survival rate increase from 35% to 65%. The time to event (TTE) will be monitored. Event is defined as relapse, tumor progression or death. Toxicity is defined as the treatment related mortality (TRM) rate, which will be evaluated within 30 days post transplant, and this rate will be compared with the 5% maximum rate.

The study statistician will be responsible for monitoring the study for safety and futility, to be implemented as follows:

Efficacy Monitoring Rule

We assume that TTE is distributed exponentially with median Q_S and Q_E, for patients treated with standard treatment BEAM and combined treatment GBM, respectively. Under a Bayesian model, we will further assume that Q_S follows an inverse gamma (IG) prior with parameter (20, 300.2) reflecting the historical data. We also assume that Q_E follows an IG prior with parameter (3.66, 42.10) with the same mean as Q_S but with a much larger variance to reflect much greater uncertainty about TTE in patients treated with GBM. The TTR data will be monitored continuously based on the following futility monitoring rule: stop accrual if Pr (> Q_S +22.8 | data) < 0.007. Specifically, the trial will be stopped early if, given the current data, it is very unlikely, ie, less than 0.7%, that the median TTE for the patients treated with GBM has at least a 22.8-month improvement over that the patients treated with standard treatment. This interim monitoring will be accomplished through the a web-based TTEDesigner software provided by the Department of Biostatistics. Assuming an accrual rate of 4 patients/month we summarize operating characteristics based on 2000 simulations in Table 2. Following Table 2, we will stop early with 90% probability if the true median TTE is 15.8 months, but only 4% probability if the true median TTE is 38.6 months (the target).

Table 2. Operating characteristics table using the early stopping boundaries specified in Table 2.

True Median TTE (months)	Probability of Stopping Early	Mean # Patients on Trial
15.8	0.90	43.2
38.6	0.04	77.9

Safety Monitoring Rule

To monitor the TRM rate, a binary outcome, there are two possible elementary outcomes. They are 1 = [treatment related death], 2 = [alive or death due to other causes]. We denote the probability vector with the experimental treatment by qE. We assume Beta (3.3, 62.7) prior on qE, which corresponds to a mean TRM rate of 5%.

The following decision criteria will be applied after a minimum of 5 patients has been evaluated, up to the 80th patient. Targeting a 5% TRM rate as a trade-off, the trial will be stopped early if

Pr[qE(TRM rate) > 5% | data] > .90

That is, if at any time during the trial we determine that we have greater than 90% posterior

probability that the experimental TRM rate is higher than 5%, we will stop the study. Stopping boundaries corresponding to this probability criterion are to terminate the trial if

(# of patients died due to treatment) / (# patients evaluated)
>/= 4/5, 5/19, 6/34, 7/50 or 8/66.

Analyses Methods

Summary statistics will be provided for continuous variables. Frequency tables will be used to summarize categorical variables. EFS and OS time will be estimated using the Kaplan-Meier estimator. For EFS analysis, patients who experience the tumor relapse, disease progression, or death will be considered to be an event. Otherwise the patients will be considered as censored. Comparison of time to event endpoints by important subgroups will be made using the log-rank test. Cox proportional hazard regression will be employed for multivariate analysis on time-to-event outcomes. 2-year relapse-free survival rate will be calculated and presented with its 95% confidence interval. TRM rate will be computed and presented with 95% confidence interval. Adverse events will be tabulated for all the patients.

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 is a non-blinded non-randomized study with no planned interim analysis. Therefore, it will not need DSMB monitoring.

Protocol Monitoring:

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

Provide a summary or schedule of interim analysis.

This protocol will be subject to continuous interim monitoring for safety and futility, as described in the Statistical section.

Protocol Monitoring Plan:

Toxicities will be scored according to CTC 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.

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.

This study is a phase 2 investigation of a regimen developed in a phase 1 trial that was itself already exempt from IND. All drugs are FDA approved.

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

	Approved Use	Proposed in this Protocol
Disease:	Ovarian cancer, lung cancer, pancreatic cancer	Hodgkin's
Dose:	1500-2000 mg/m^2	1875 mg/m^2
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? No

Radioactive Material:

Does this study involve the administration of radioisotopes or a radioisotope labeled agent? Click here for help	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?	No

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