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Department of Hematology and Hematopoietic Cell Transplantation

TITLE: Phase I/II Study of Intravenous (IV) Busulfan and Etoposide (VP-16) Combined with Escalated Doses of Large Field Image-Guided Intensity Modulated Radiation Therapy (IMRT) using Helical Tomotherapy as a Preparative Regimen for Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) for Patients with Advanced Myeloid Malignancies

CITY OF HOPE PROTOCOL VERSION:	**IRB # 05013**	**Protocol Date: 06/29/11**
Amendment 01		Version 01
Amendment 02		Version 02
Amendment 03		Version 03
Amendment 04		Version 04
Amendment 05	Title Page dated 1/29/10	Version 05
Amendment 06	Protocol Dated 07/29/2009	Version 06
Amendment 07	Title Page dated 02/07/2011	Version 07
Amendment 08	Protocol dated 5/23/11	Version 08
Amendment 09	Protocol dated 6/29/11	Version 09
Amendment 10	Title Page dated 01/15/13	Version 10
Amendment 11	Title Page dated 09/25/13	Version 11
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Amendment 13 at Continuation	Title Page dated 06/23/17	Version 13
Amendment 14 at Continuation	Protocol dated 06/29/11 (tp)	Packet: 14

HISTOLOGY: Myeloid Malignancies
STAGE: Advanced
MODALITY: Allogeneic BMT
TYPE: Phase I/II

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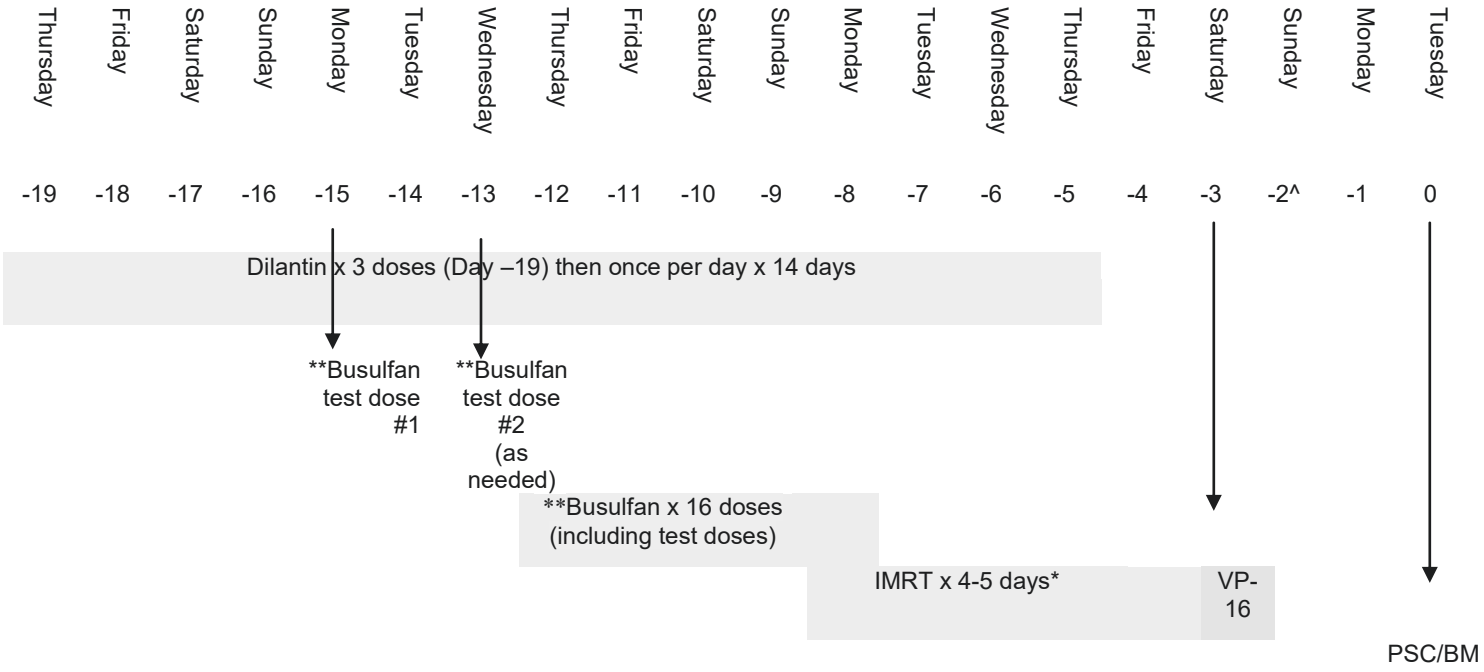
SCHEMA



*: IMRT = Image-Guided Intensity Modulated Radiation Therapy
IMRT to begin on Monday and delivered over 4-5 days depending upon IMRT dose
The start of IMRT can be delayed up to 24 hours to accommodate any holiday closures by the Department of Radiation.
** When IMRT is given over 4 days (8 doses), Busulfan test dose #1 will start on Day -14, test dose #2, if needed, will be given on Day -12 and the remaining busulfan doses will be given starting on Day -11.
** When IMRT is given over 5 days (>8 doses), Busulfan test dose #1 will start on Day -15, test dose #2 (if necessary) will be given on Day -13 and the remaining busulfan doses will be given starting on Day -12.
^ If tacrolimus and sirolimus are used for GvHD prophylaxis, their administration will begin on Day -2.

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1.0 OBJECTIVES

This study will be initiated as a phase I trial in order to be certain that there are no unpredicted toxicities by the incorporation of intensity modulated radiation therapy (IMRT) with intravenous (IV) busulfan [targeted to AUC (area under curve) of 700-900] and etoposide (VP-16) as a preparative regimen for allogeneic hematopoietic stem cell transplantation (HSCT). Based on our evaluation of this treatments safety and feasibility, a phase II trial of 30 patients will be performed in subsequent years focused on overall survival, relapse-free survival, event-free survival, treatment related mortality, relapse and toxicity. Early stopping rules will be incorporated into the phase II portion for safety, however, there will be no early stopping based on efficacy.

The objectives of the phase I portion of this study are:

1.1 To establish the maximum tolerated dose (MTD) of large field image-guided IMRT, using helical tomotherapy, when given in combination with IV busulfan and VP-16 as a preparative regimen for allogeneic hematopoietic stem cell transplantation (HSCT) from an HLA-identical sibling in patients with:

- advanced myeloid malignancies with a disease status of >2nd remission, induction failure, or relapse
- chronic myeloid leukemia in blast crisis
- myelodysplasia, refractory anemia with excess blasts (RAEB).

1.2 To describe the toxicities at each dose level studied.

1.3 To estimate the radiation doses to the whole body, normal organs, and bone marrow through serial imaging studies following the administration of IMRT.

The objectives of the phase II portion of the study are:

1.4 To estimate the overall survival probability, disease free survival probability, and relapse rate associated with this preparative regimen.

1.5 To characterize the treatment related mortality and toxicity profile (early/late) associated with this regimen.

1.6 To descriptively compare the outcomes of patients treated on this protocol to a comparable patient population conditioned with whole body radiation.

2.0 BACKGROUND AND HYPOTHESES

During the last 20 years clinical bone marrow transplantation from a histocompatible sibling donor has evolved into an important treatment modality for patients with acute lymphoblastic leukemia, acute myeloid leukemia and chronic myeloid leukemia. If the transplant procedure is performed in first complete remission/chronic phase of acute leukemia/chronic myeloid leukemia, approximately 50-70% of patients become disease free long-term survivors.[1-8] In contrast, the chances for an ultimately successful outcome of bone marrow transplantation drops to 10-40% if this is performed during second or subsequent complete remission, during relapse of acute leukemias, or while patients with chronic myeloid leukemia are in accelerated or blast phase of this disease. In the latter group of patients the probability of leukemic relapse is in the range of 40-70%.[9-16] Many

transplant centers have performed several phase I-II trials of preparative regimens using alternative chemotherapeutic agents or methods of administering total body irradiation (TBI). Some of these studies suggest a decrease in the post-transplant relapse rate that are often associated with increased transplant related morbidity and mortality from regimen related toxicity.[17-20] At the City of Hope a phase I/II trial was conducted in 1986 to determine the efficacy of substituting etoposide (VP-16) for cyclophosphamide in combination with fractionated total body irradiation (FTBI). This trial was done in 33 patients with acute leukemia beyond first remission, and resulted in a 43% long-term disease free survivorship. Despite this improved survival compared to previous studies there still is significant relapse rate, particularly in patients with advanced leukemia. This regimen has subsequently been utilized to treat 100 patients with acute leukemia in remission. There was only one case of fatal veno-occlusive disease; otherwise the regimen was well tolerated.[21] Studies combining busulfan and cyclophosphamide as a preparative regimen for patients with advanced hematological malignancies have been reported to result in similar or superior outcomes when compared with standard cyclophosphamide and TBI regimens, suggesting that busulfan has important anti-leukemic effects. A randomized Southwest Oncology Group study (SWOG) comparing busulfan, cyclophosphamide with FTBI VP-16 showed 20% disease free survival for patients transplanted with advanced leukemia.[22] At City of Hope a phase I study was conducted utilizing escalating doses busulfan in combination with fixed doses of FTBI and VP-16 in an attempt to decrease the relapse rate in those patients transplanted for advanced hematological malignancies. The rationale behind the study was that we combined three non-cross resistant anti-leukemic agents with non-overlapping extramedullary toxicities. An in vitro synergy has been demonstrated between busulfan/VP-16 and busulfan/VP-16 has been proven to be an effective regimen for relapsed leukemia and for allogeneic bone marrow transplant (ABMT) for AML in first and second remission.[23,24] The dose limiting toxicity (DLT) occurred at 12mg/kg the maximum total dose (MTD) was defined at 11mg/kg. At this dose level median first dose AUC for these patients was 892μM*min (460-1267). With a median follow-up of 11.5 months, the disease-free survival is 32%, and the probability of relapse is 40%. The only variable predictive of a disease-free survival and relapse was the busulfan dose of 7-8 mg/kg. In this phase I study there was a wide variability of the AUC of busulfan due to the variability of absorption of oral busulfan. An AUC of 700-950 showed a trend to a decreased relapse rate and improved disease free survival.

A phase II study utilizing intravenous (IV) busulfan was conducted at City of Hope which has resulted in Food and Drug Administration (FDA) approval of IV busulfan and it is proposed to substitute IV busulfan which has been shown to have more predictable pharmacokinetic properties than the oral preparation resulting in a better toxicity profile.[25,26,27]

At City of Hope 15 patients with poor risk acute myeloid leukemia have been treated with allogeneic HSCT utilizing targeted Busulfan/FTBI and VP-16 as conditioning regimen and Mycophenolate + Cyclosporin for graft versus host disease (GVHD) prophylaxis between 1999 and December 2003. The disease free survival and probability of relapse at 18 months is 50% and 20%, respectively. The non-relapse mortality from infectious causes and chronic GVHD is 24%. Most patients treated on the protocol developed significant mucositis and gastrointestinal toxicity.

2.1 Rationale for Increasing Dose of Radiation

Two randomized and one large non-randomized trial, have explored the importance of radiation dose on post transplant relapse rates. In total, 71 patients with Acute Myeloid Leukemia (AML) in first remission were treated with cyclophosphamide and either 12 Gy (n=34) or 15.75 Gy (n=37) of TBI followed by HLA-matched sibling transplantation and methotrexate and cyclosporine as GVHD prophylaxis. The relapse rate in the group receiving the lower TBI dose was 35% compared to 12% with the higher TBI dose (P=0.06)[29]. In a similar prospective randomized trial in patients with chronic myeloid leukemia (CML) in chronic phase, the relapse rate in the 57 patients treated with the lower TBI dose was 25% compared to 0% in the 59 recipients of the higher TBI dose (P=0.008)[30]. In both studies, non-relapse mortality was higher with the higher TBI dose, thus balancing the reduction in relapse rates, with a result that in neither study overall survival was improved.

Marks et al recently analyzed the outcome of 502 patients reported to the International Bone Marrow Transplant Registry (IBMTR) following matched sibling transplantation for acute lymphoblastic leukemia (ALL) in first and second remission. They concluded that the TBI dose was the most significant factor they could identify for predicting relapse rates. Doses of TBI in excess of 13 Gy resulted in 40% reduction in the chance of relapse (P=0.01), and also translated into a 37% reduction in the risk of death[31].

2.2 Rationale for Large Field Image-Guided Intensity Modulated Radiation Therapy (IMRT)

Rapid advances in computer and medical imaging technologies have resulted in the ability to deliver radiotherapy with greater precision and conformality. External beam radiotherapy has traditionally relied on radiologic imaging to direct therapy to appropriate anatomic regions. The integration of computerized tomography (CT) imaging into radiation treatment planning, allows for a three dimensional (3D) view of each patient's tumor relative to dose-limiting adjacent normal organs, allowing for customized beam shaping, beam orientation and dose conformality. The use of 3D conformal radiotherapy allows for further escalation of dose, which has resulted in higher tumor control, while maintaining risks and side effects at acceptable levels.

Intensity modulated radiation therapy (IMRT) has opened a new era in radiation oncology. By delivering therapy from multiple directions using multiple segmented or modulated beamlets, one can now sculpt radiation doses to fit the unique shape of each patient's tumor, optimizing radiation delivery to complex volumes and regions of the body. Some compare IMRT to "painting" radiation with a finer brush, where more precise, conformal and sophisticated dose patterns are now possible. This has also resulted in a greater degree of conformal dose avoidance of adjacent normal organs. Dose escalation is now possible with IMRT, which was not possible with technology just a decade ago. For example, radiation doses for prostate cancer, which have been limited to approximately 7000 cGy with conventional technologies, are now >8000cGy using IMRT. As a result, a significant improvement in tumor control and a reduction in bladder and rectal toxicities have been reported.[(32)]

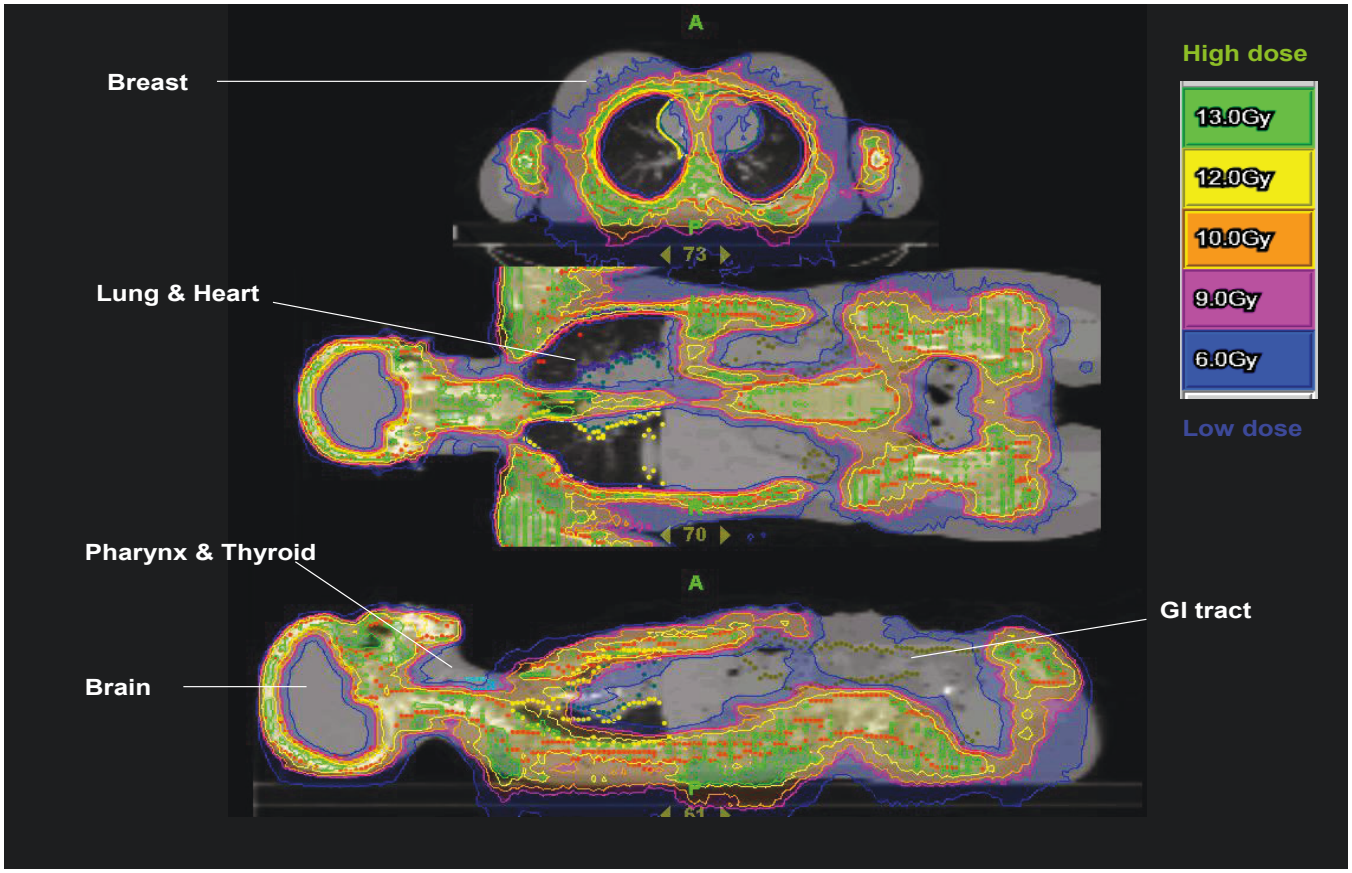
Helical tomotherapy (HT) represents a convergence of technological advances in CT image-guided radiation therapy (RT) and IMRT. HT is a FDA approved radiation therapy delivery device, which is a marriage of spiral CT and IMRT technology. Specifically, a 6 MV linear accelerator is mounted on a CT ring gantry and rotates around the patient as the patient translates through the ring. The treatment fan beam is segmented using a 64-leaf collimator. Each leaf casts a 0.6 mm width shadow at 85 cm isocenter distance with

the fan beam, which varies in width (slice thickness) from 0.5 to 5cm. The minimum voxel or beamlet size is therefore 5 x 6 mm. The maximum couch length is 160 cm. Therefore the maximum target size is up to 40 cm wide by 160 cm long. By rapid opening and closing of leaves as a function of gantry angle while the patient slides trough the ring, helical tomotherapy provides unprecedented ability to sculpt radiation doses to large complex shaped target regions while simultaneously avoiding dose to normal organs.[33,34] Grigorov et al.[35] evaluating HT treatment plans for prostate cancer, demonstrated rapid drop-off of dose around the target (prostate gland) in all directions resulting in excellent sparing of rectum, bladder and femoral heads superior to prior IMRT techniques. Scrimger et al[36] predicted that for select patients with lung cancer, tumor doses as high as 16,000 cGy will be achievable while maintaining normal lung doses (and therefore risks) at comparable levels as with conventional delivery methods, which are limited to doses of 6,000 cGy to the tumor in most patients.

In addition, an array of detectors mounted on the same rotating gantry and positioned directly opposed to the beam source, gives the HT delivery system two unique capabilities not found on any other delivery systems. First, these detectors allow for the generation of megavoltage CT (MVCT) images using the 6 MV beam. Resolution and contrast of MVCT is more than adequate to easily distinguish tissue planes and organ boundaries.[33] This allows the HT system to automatically align beam orientation to anatomic external landmarks and internal organs in 3 dimensions prior to each daily session, improving the precision of radiation delivery. Second, these same arrays can be used to monitor output of the beam as it exits through the patient, providing an additional level of dose verification in 3 dimensions. In the future, it is anticipated that future software and hardware modifications will allow for this type of 'adaptive radiotherapy' to occur in real time, constantly modulating beam output to account for minute-by-minute variations in tumor and organ motion and delivered dose.

The advent of HT brings for the first time to the clinic the potential to deliver highly conforming dose distributions to large complex target shapes. For example, with HT shaping the dose to the entire pleural surface, while sparing lung parenchyma is now possible for patients with mesothelioma. At the City of Hope (COH), TBI is often used as part of the preparatory regimen for many patients undergoing bone marrow transplants. Although TBI will effectively treat the target region which includes the marrow space and, in some patients, extramedullary hematopoietic sites, such as spleen and lymph nodes, TBI also delivers the same dose to all other normal organs resulting in dose-limiting toxicity, such as nauseas and vomiting, mucositis and pneumonitis. Working with collaborators at the University of Wisconsin and Tomotherapy, Inc. (manufacturers of HT), we have recently evaluated the feasibility of delivering conformal radiation doses to just the skeletal bone containing the marrow spaces as a possible alternative to TBI. Total marrow irradiation (TMI) using HT would dramatically reduce dose to normal tissues, reducing short-term and long-term toxicities. Using whole body CT images captured on the COH Radiation Oncology Picker CT treatment planning system, normal organs and target skeletal bone compartments were contoured. After defining appropriate target and organ dose constraints, inverse planning using the HT planning station was used to generate dose distributions and dose volume histograms.

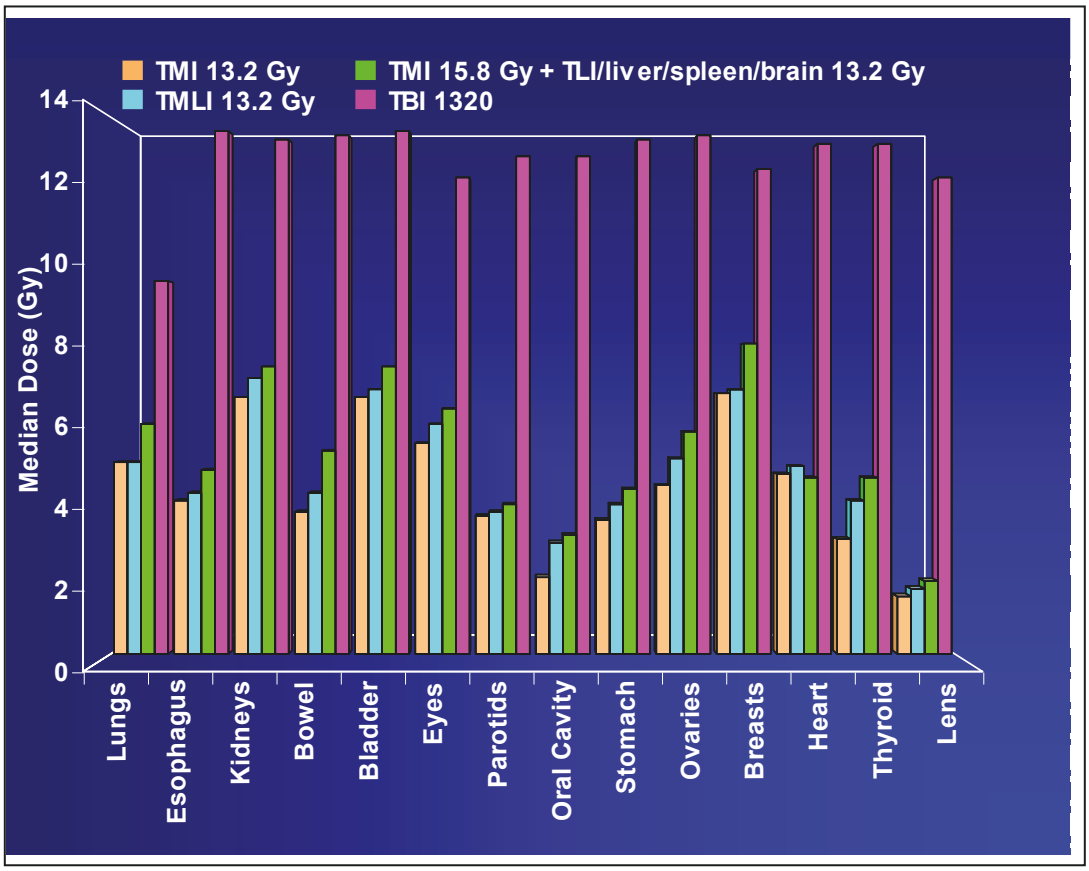
An example of TMI dose distribution plan is shown in the following figure:

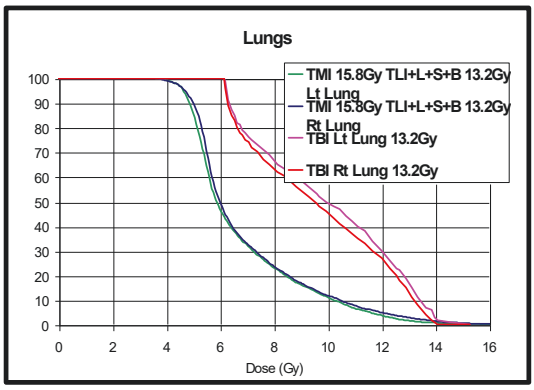


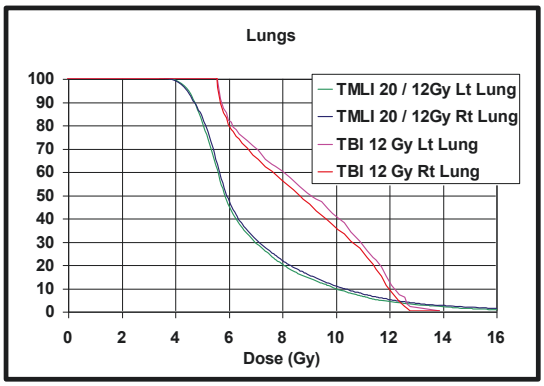
In this example the prescribed dose is 12.0 cGy, which will take an estimated 23 minutes to deliver by HT. Demonstrated is conformality of the dose to the skeletal bone and a significant reduction in dose to normal organs, such as brain, oral cavity, oropharynx, lung, heart, soft tissue and gastrointestinal (GI) tract.

The prescription dose to the target volume will be prescribed to cover 85% of the target volume.

Recently studies have been performed using the COH tomotherapy treatment planning system to perform comparative dose and dose-volume histogram studies for the following scenarios: 1) 1320 cGy TMI (total marrow or skeletal bone IMRT); 2) 1320 cGy TMLI (TMI + liver, spleen, and sanctuary sites such as brain also as target regions); 3) 1580 cGy TMLI; and 4) 2000 cGy TMLI (2000 cGy TMI + liver, spleen, sanctuary sites, rib cage and skull at 1200 cGy). For the last scenario, the rib and skull bones were kept at 12 Gy to allow for greater dose uniformity within the immediately adjacent liver, spleen and brain. The graph below compares the median doses to normal organs, which are all substantially lower than conventional TBI. Also shown for comparison are dose-volume histograms for lung for scenarios 1,3 and 4. For each scenario of dose escalation lung DVHs are to the left of the DVH for conventional TBI predicting for lower risk of pneumonitis.







Such dose sparing or conformal dose avoidance of normal tissues should result in clinically important reductions in acute toxicities and potential to reductions in long-term complications such as hypothyroidism, pneumonitis, second malignancy induction, and, in the pediatric population, effects on growth and development. Finally, reduced morbidities should allow for escalation of the dose to the target compartment to levels not achievable with conventional TBI, which has the potential of increasing control rates. The starting TMLI dose level will be 1200 cGy at 150 cGy per fraction BID with a minimum 6-hour interval between fractions. The TMLI dose will be increased to 1350 (150 x 9), 1500 (150 x 10), 1750 (175 x 10) and 2000 (200 x 10) cGy. Conformal avoidance of dose is planned for the following organs: lung, kidneys, heart, thyroid gland, oral cavity, oropharynx, lens, GI tract, breasts, esophagus, and parotids. The ribs, liver and spleen dose of TMLI will be fixed at 1200 cGy.

3.0 DRUG INFORMATION

3.1 Busulfan (Myleran)

3.11 Mechanism of Action: Busulfan is a bi-functional alkylating agent. In aqueous media, busulfan hydrolyses to produce reactive carbonium ions that can alkylate DNA.

3.12 Formulation and stability: Busulfan injection is a sterile, pyrogen-free solution provided in a mixture of dimethylacetamide (DMA) and polyethlyeneglycol 400 (PEG 400). It is supplied in 10-ml single use ampules at a concentration of 6-mg Busulfan per ml. Each ampule contains 60mg of Busulfan in 3.3 ml of DMA and 6.7 ml of PEG 400. When diluted in normal saline or D5W to a concentration of 0.5mg/mL, the resulting solution must be administered within eight (8) hours of preparation; including the 2 hours of infusion of the drug.

Stable at 4º C for at least twelve months. Ampules should be stored refrigerated at 2-8º C. Do not freeze. Ampules may be stored for up to seven days at room temperature.

Solution preparation: prepare the Busulfan solution as follows: Use sterile, non-pyrogenic, disposable containers, syringes, needles, stopcocks, and transfer tubing, etc. Calculate the amount of drug to be administrated based on the dosage and the patient's body weight.

Prepare a solution of 0.9% sodium chloride injection USP (normal saline) calculated Busulfan dose in ml from the step above.

Break off the top of the ampule and remove the calculated volume of Busulfan from the container by using a syringe fitted with a filter needle or equivalent. Transfer the contents of the syringe into the calculated amount of either normal saline or D5W making sure that the drug flows into and through the solution. Mix by inverting the bag.

3.13 Administration: Each dose of the drug will be given by slow central intravenous infusion over 2 hours. **Caution: Do not administer as an IV push or bolus.**

3.14 Supplier: This drug is commercially available. This drug is manufactured by Orphan Medical Inc.

3.15 Toxicity: Toxicities from busulfan include:

a. Severe bone marrow hypoplasia, which would be fatal without administration of bone marrow, stem cells.
b. Nausea and vomiting which can be decreased by the use of sedation and anti-emetics.
c. Stomatitis and diarrhea which can be treated symptomatically with fluid replacement and atropine or diphenoxylate H C1.
d. Pulmonary fibrosis characterized by delayed onset of cough, shortness of breath and low-grade fever.
e. Hepatic damage, which can occur in combination with cytoxan or as a single agent and can result in significant hepatic toxicity which, can be fatal.
f. Temporary hyperpigmentation of the skin and nail bed changes.
g. Grand mal seizures which can be prevented by the prophylactic administration of Dilantin.

3.2 VP-16 (VP-16-213) (Etoposide) (Vepesid)

3.21 Chemistry: VP-16 is a semi-synthetic podophyllotoxin derivative from the plant podophyllum pletatum, has anti-neoplastic properties in experimental animals and in man. The empiric formula C_{29} H_{32} 0_{13} has a molecular weight of 588.

3.22 Mechanism of Action: The epipodophyllotoxin exert phase-specific spindle poison activity with metaphase arrest, but in contrast to the vinca alkaloids, have an additional activity of inhibiting cells from entering mitosis. Suppression of tritiated thymidine, uridine, and leucine incorporation in human cells in tissue culture suggest effects against DNA, RNA and protein synthesis.

3.23 Animal Tumor Data: Significant anti-tumor effect has been demonstrated in L-1210, mouse sarcoma 37 and 180, Walker carcinosarcoma and Erlich ascites tumor. With the L 1210 system, activity was schedule-dependent, having greater effect with a twice a week administration than with daily dosing or the administration of single large doses. The drug is active given intraperitoneally or orally in L 1210. No effect was demonstrated intracerebrally inoculated L 1210.

3.24 Animal Toxicology: The predominant toxicities of VP-16 in animal studies involve the hematopoietic system, with toxicity to the liver and GI tract occurring only at doses producing profound myelosuppression. Anemia, leukopenia, and lymphoid involution occur in mice, rats and monkeys. Acute toxicity investigations have been complicated by the toxicity of the solvent system. The LD-50 of the solvent plus drug approached that of the solvent alone. Immuno-suppressive effects occur with an inhibition of antibody production in mice and monkeys, and prevention of experimental allergic encephalomyelitis in rats (cell mediated immunity).

3.25 Human Toxicology: Reversible myelotoxicity has been uniformly observed to be the major toxicity of VP-16 and to represent the only clinically significant side effect. Following a single IV injection, peak myelotoxicity occurs at 7 to 9 days. Following daily IV injections for 5 to 7 days, myelotoxicity is maximal between 12 to 16 days from the initiation of therapy. Bone marrow suppression is mainly manifested as granulocytopenia with thrombocytopenia and anemia occurring to a lesser extent. Transient, modest nausea, usually without vomiting, is common. Occasional alopecia is reported. VP-16 does not produce stomatitis, phlebitis, neurotoxicity, hepato-toxicity or nephro-toxicity. Hypotension and anaphylaxis are occasional side effects. Hypotension can be managed by infusing the drug over at least a 30 minute period. Occasionally, fever may be a result of VP-16 administration.

3.26 Pharmaceutical Data: Formulation: 100 mg of VP-16 is supplied as 5 ml of solution in clear ampules for injection. Each ampule also contains anhydrous citric acid 10 mg, benzylalcohol 150 mg, polysorbate 80 purified 400 mg, polyethylene glycol and absolute alcohol. The contents of the ampule are non-aqueous and must be diluted with 20 to 50 volumes of sodium chloride injection USP. The time before precipitation depends on concentration.

Dilution	Time
1:20	30 minutes
1:50	3 hours
1:100	6 hours

3.27 Storage and stability: The drug is available as a box of 10 ampules that are stored at room temperature. Each ampule should be kept in the box to protect it from light. VP-16 is less stable in 5% Dextrose injection and precipitation is reported. VP-16 has a minimum infusion time of 30 minutes to reduce hypotension.

3.28 Supplier: VP-16 is commercially available.

4.0 STAGING CRITERIA:

4.1 Definition of Disease Phases in Chronic Myeloid Leukemia

Chronic Phase

1. No significant symptoms, which are not readily controlled by conventional doses of hydroxyurea or busulfan.

2. None of the features of accelerated phase or blastic phase. (Note: Granulocytic hyperplasia and the Philadelphia chromosome may be present in the bone marrow).

Accelerated Phase (any one or more of the following criteria)

1. White blood count (WBC) difficult to control with conventional use of busulfan/hydroxyurea in terms of doses required or shortening of intervals between courses.

2. Rapid doubling of WBC ($\leq$ 5 days).

3. $\geq$ 10% blasts in blood or marrow.

4. $\geq$ 20% blasts plus promyelocytes in blood or marrow.

5. $\geq$ 20% basophils plus eosinophils in blood.

6. Anemia or thrombocytopenia unresponsive to busulfan/hydroxyurea.

7. Persistent thrombocytosis ($\geq$ 1,000,000/ 1) unresponsive to conventional doses of hydroxyurea or busulfan.

8. Additional chromosome changes (evolving new clone).

9. Increasing splenomegaly unresponsive to conventional doses of hydroxyurea or busulfan.

10. Development of chloromas or myelofibrosis.

11. Patients in a second (or subsequent) chronic phase after blast crisis.

Blastic Phase/Blast Crisis

1. ≥ 30% blasts plus promyelocytes in the blood or bone marrow.

5.0 ELIGIBILITY CRITERIA

5.1 Inclusion Criteria

5.1.1 Patients with the following diagnoses are eligible for this study:
- advanced myeloid malignancies with a disease status of >2nd remission, induction failure, or relapse
- chronic myeloid leukemia in blast crisis
- myelodysplasia, subtype: refractory anemia with excess blasts (RAEB)

5.1.2 All candidates for this study must have a HLA (A, B, C, DR) identical sibling who is willing to donate bone marrow or primed blood stem cells or a 10/10 allele matched unrelated donor or minor mismatches as per BMT SOP that allows Tacrolimus and Sirolimus to be given for GVH prophylaxis. All ABO blood group combinations of the donor/recipient are acceptable since even major ABO compatibilities can be dealt with by various techniques. (Red cell exchange or plasma exchange).

5.1.3 Prior therapy with VP-16, busulfan, hydrea and gleevec are allowed.

5.1.4 Patients must be older than 6 years and the upper age limit for this study is 55 years.

5.1.5 A cardiac evaluation with electrocardiogram and MUGA or echocardiogram is required for all patients. Patients must have an ejection fracture of greater than or equal to 50%.

5.1.6 Patients must have a serum creatinine of less than or equal to 1.2 or creatinine clearance > 80ml/min.

5.1.7 A bilirubin of less than or equal to 1.5. Patients should also have an SGOT and SGPT less than 5 times the upper limit of normal.

5.1.8 Pulmonary function tests including DLCO will be performed. FEV_1 and DLCO should be greater than 50% of predicted normal value.

5.1.9 Time from the end of last induction or reinduction attempt should be greater than or equal to 21 days.

5.1.10 A signed (IRB approved) informed consent document is required. The patient, donor family member, and transplant team (physician, nurse, and social worker) meet together at least once prior to starting the transplant procedure to review all

pertinent risk/benefit information as part of the consenting process. Alternative treatment modalities are also discussed at this meeting.

5.2 Exclusion Criteria

5.2.1 Prior radiation therapy/exposure that prevents the patient from receiving IMRT. (Determination will be made by the Radiation Oncologist.)

5.2.2 Patients who have previously undergone a blood/marrow transplant and now have relapsed disease.

5.2.3 Patients with a psychological or medical condition that the treating physician deems unacceptable to proceed to allogeneic bone marrow transplant.

5.2.4 Pregnancy

5.2.5 EKG showing ischemic changes or abnormal rhythm and echocardiogram showing ejection fraction <50% or abnormal wall motion.

5.3 Donor Inclusion/Exclusion Criteria

5.3.1 Any sibling donor who is histocompatible with the prospective recipient will be considered a suitable donor.

5.3.2 Donors will be excluded if for psychological or medical reasons they are unable to tolerate the procedure.

5.3.3 Donor should be able to donate peripheral blood stem cells or bone marrow.

6.0 TREATMENT PLAN

All patients will have a right atrial catheter, hickman type inserted. This catheter will be used for collection of blood specimens, administration of drug, bone marrow, blood components, and for hyperalimentation.

6.1 Pre-transplant evaluation will be performed within four weeks of beginning treatment except for the following: 1) Bone marrow aspirate and biopsy + cytogenetics within 14 days of starting treatment, 2). Complete blood count (CBC), differential, platelets, comprehensive metabolic panel within 5 days of starting treatment.

a. Prior to admission patient will have a complete history and physical examination performed. Special attention will be given to prior chemotherapy, height, weight and body surface area should also be noted.

b. Patients will have the following laboratory tests performed:

i. CBC with diff platelets

ii. Sodium, potassium, chloride, bicarbonate or total carbon dioxide, BUN, creatinine, Ca, Mg, Phosphorous, total bilirubin, total protein, albumin, SGPT, SGOT, LDH, alkaline phosphatase, glucose.

iii. Urine analysis
HIV test

Hepatitis A, B + C
24-hr urine for creatinine clearance
CMV, HSV – HZV ab
Immunoglobulin levels

iv. 24-hour urine collection for creatinine clearance.
v. Chest x-ray and electrocardiogram (EKG)
vi. CT scan of chest, abdomen and pelvis.
vii. Pregnancy test

c. Initial coagulation studies prothrombin time, APTT.
d. MUGA scan or echocardiogram
e. Pulmonary function tests, including DLCO
f. A bone marrow aspirate and biopsy, and cytogenetics needs to be done within 2 weeks of admission (if bone marrow not aspirable and > 20% blasts in blood this may be done on peripheral blood sample).
g. Patients with acute leukemia or chronic myeloid leukemia in blast crisis will have a lumbar puncture performed. Methotrexate (10mg/m^2 but not more than a total dose of 12mg) will be administered intrathecally. The spinal fluid will be examined for the presence of malignant cells. Those patients who had leukemic central nervous system (CNS) involvement prior to the time of admission before transplantation will receive five weekly intrathecal methotrexate injections with the dose described above from the time patients platelet count is greater than 75,000 to day 100, then monthly intrathecal methotrexate injections with the dose described above between day 100 and 12 months after transplantation. The initial spinal tap will only be performed if patient's platelet count can be kept above 75,000.

6.2 Preparative Chemotherapy Regimen
(Note: Patient to sign consent form before starting Dilantin.)

Thursday/Day -19	Begin dilantin 300mg/p.o. t.i.d. times 1 day, then 300mg/p.o./IV daily times 14 days.
Monday/Day -15	Admission or outpatient, dilantin blood levels will be checked and dose adjusted as needed to meet therapeutic range. Further adjustments if clinically indicated. Busulfan test dose administered at 6:00 to 8:00 a.m. as a single dose. The IV dose is calculated as follows:

1. Body surface area (BSA) is calculated by the equation:

$$BSA = \sqrt{\frac{(\text{Actual body wt. (kg)} \times \text{height (cm)}}{3600}}$$

2. 22mg/m^2 IV Busulfan will be given over 2 hours. Blood levels will be obtained with the first dose as per appendix 1 and will be performed per current Hematopoietic Cell Transplant Program Clinical Manual of Standard Operating Procedures.

Tuesday/Day -14 Busulfan AUC will be calculated per current Hematopoietic Cell Transplant Program Clinical Manual of Standard Operating Procedures. The resulting AUC will be used to determine the dose required to achieve an AUC of 800 μM* min according to the following formula:

$$\text{Adj dose} = \text{Current dose} \times \frac{800\mu\text{M x min}}{\text{test dose AUC}}$$

The maximum dose given will not exceed 32mg/m^2. There is no limit on dose reduction Busulfan dose will only be adjusted for AUC's <700 or >900 μM*min.

Wednesday/Day -13 The adjusted dose Busulfan dose will be given at 6 a.m. and blood levels will be repeated. Further dose adjustments will be performed if AUC >1000.

Thursday/Day -12 Patient admitted to Bone Marrow Transplant (BMT) unit or receive further dose of Busulfan in clinic.

Busulfan dosing restarted at 12-noon if only one test dose of busulfan administered and at 6 p.m. if two doses administered. The adjusted dose is repeated every 6 hours for a total of 16 doses (including the test doses).

Monday/Day -8 See Section 6.5 for treatment planning and delivery of total marrow and lymphoid irradiation.

Saturday/Day -3 VP-16 30mg/kg based on adjusted ideal body weight will be administered.

Tuesday/Day 0 PSC reinfusion/or BM infusion

PSC Collection as per current Hematopoietic Cell Transplant Program Clinical Manual of Standard Operating Procedures.

Toxicities of the marrow infusion are very rare. Volume overload may be prevented by removal of plasma from the marrow aspirate or by phlebotomy of the recipient prior to marrow infusion. Pulmonary emboli are theoretically possible and would require management with 02 or IPPB. However, our clinical observations over the last 20 years indicate that pulmonary embolism in this clinical setting does not occur at any increased rate. The most frequently encountered problem is that of chills, hives, and fever. Those allergic reactions occur rarely (in 1 to 2%) and can be prevented by intravenous injections of dyphenhydrimine 25mg and hydrocortisone (50mg) prior to the bone marrow infusion.

6.3 Graft Versus Host Disease (GVHD) Prophylaxis and Treatment

6.31 GVH prophylaxis regimen will consist of the best available regimen excluding methotrexate.

6.32 If moderate to severe graft-versus-host disease occurs (Grade II-IV), patients will be treated with the administration of higher doses of methyl-prednisolone, anti-thymocyte globulin, etc.

6.33 Graft-versus-host disease will be graded according to previously defined criteria (Appendix III, IV).

6.4 Supportive Care will be given as per current Hematopoietic Cell Transplant Program Clinical Manual of Standard Operating Procedures.

6.5 Treatment Planning and Delivery of Total Marrow and Lymphoid Irradiation (TMLI).

6.5.1. TMLI will be delivered using Helical Tomotherapy. Tomotherapy is an image-guided IMRT delivery device and is the only device currently capable of delivering the proposed TMLI radiation therapy. Therefore, for this trial all patients will be treated using the Tomotherapy system. In addition, all treatment planning will take place on the Tomotherapy HiArt treatment planning system.

6.5.2. Simulation. All patients will undergo CT simulation with scanning from the top of the scalp to the level of the distal femurs. Prior to simulation, the patients will be fitted for an immobilization cast they will be treated in. Aquaplast facemask will be utilized for head positioning. A full-body immobilization cast will also be used (Vaclok). CT scans will be acquired at full inspiration, full expiration, and mid-inspiration.

6.5.3. Treatment Planning. Treatment planning will take place on the Tomotherapy HiArt treatment planning system. The following organs will be contoured: lungs, heart, small and large intestine, kidneys, orbits, lenses, oral cavity, bladder, parotid glands, stomach, ovaries (if clipped for localization), testes, liver, spleen, esophagus, bone, and major lymph node chains. The target regions will include the bone, major lymph node chains, liver, spleen, testes, and brain. All other contoured organs will be treated as avoidance structures. Contouring for lungs, spleen, and kidneys will take into account organ position as full inspiration, full expiration, and mid-inspiration. The bone compartment will be contoured such that the entire ribcage bilaterally will be contoured as a separate region of interest. The skull will also be contoured as a separate region of interest. The gross tumor volume (GTV) will be the planning tumor volume (PTV). It is recommended that the treatment planning use a 25 mm slice thickness and a pitch of a least 0.35. A minimum of 80% of the targeted region is to receive the prescribed dose with a primary objective being to reduce the median dose (D_{50}) and maximum dose of which 90% of the organ receives (D_{90}) to a minimum. The table below provides guidelines for treatment planning parameters.

6.5.4. Delivery of Treatment Fraction. Patient is positioned on the treatment couch in the immobilization device with Aquaplast head mask in place. Treatment is delivered on the Tomotherapy unit in the cranial causes direction (Patient travels through the Tomotherapy unit head first). Prior to delivery of therapy, a mega voltage CT (MVCT) scan is performed on the Tomotherapy unit. It is recommended that scanning be over a segment of at least 5 cm, and the initial scans in the head region travel through the entire orbital and oral cavity regions. The MVCT is then

aligned with the treatment planning kilovoltage CT (KVCT) scan using the Tomotherapy system. Therapy then commences treating from the top of the scalp to approximately the sternal notch. At that point in time, a second MVCT is obtained thru the level of the kidneys. Alignment of MVCT to KVCT again occurs and treatment of the rest of the upper torso and abdomen and pelvic regions is accomplished. If deemed appropriate by the M.D., the physicist and/or radiation therapist, a third MVCT scan may be acquired through the pelvic region prior to treating through the pelvis.

The Tomotherapy TMLI inferior border will be clearly identified and marked (tattooed) prior to start of therapy. This marked inferior border of the TMLI field will serve as the "matchline" for matching the AP and PA lower extremity fields used to treat the distal femur and rest of the distal lower extremities. The AP ad PA fields will treat the lower extremities through equally weighted opposed AP/PA fields to the same dose as the TMI fraction and be prescribed to midplane.

6.5.5. The Phase 1 portion of this study will escalate the dose of TMLI through five planned dose levels as described in the section 7.0. For patients receiving two fractions on the same day, there must be a **minimum of six hours between fractions.**

As dose is escalated to the TMI target region, the ribs, liver, spleen, brain and skull will be fixed at 12 Gy (See Appendix XII).

7.0 STUDY DESIGN AND RULES FOR DOSE ESCALATION

This is a single center phase I/II trial that consists of dose escalation (phase I portion), followed by expanded enrollment at the MTD (phase II portion). Registration and assignment to the dose level will be done at City of Hope (see section 11.0). The rules for dose escalation, dose expansion and termination of escalation are given in sections 7.1 and 7.2. Study design considerations and targeted response rates for the phase II portion of the trial are given in sections 10.2-10.4.

The goal of the phase I study is to evaluate the toxicity results for the combination of intensity modulated radiation therapy (IMRT) with IV busulfan [targeted to AUC (area under curve) of 700-900] and VP-16 as a preparative regimen for hematopoietic stem cell transplantation from an HLA-identical sibling or HLA-fully-matched unrelated donor. For the phase I portion of the study, the assessment will be done in two strata:

- Stratum 1: Adult patients (≥18 years, ≤55 years) with advanced myeloid malignancies or high-risk myelodysplasia.
- Stratum 2: Pediatric patients (6-17 years) with advanced myeloid malignancies or high-risk myelodysplasia.

The primary endpoint for the phase I portion of the study is the determination of the MTD in five doses to be tested in each of the above stratum.

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7.1 Dose limiting toxicity (DLT)

Toxicities will be recorded using two distinct grading systems; the modified Bearman Scale (Bearman, S., et al, JCO, Vol 6, No 10 (Oct), 1988, pp1562-1568. See appendix X for details.) and the NCI CTCAE 3.0 Scale.

Generally, the modified Bearman Scale will be used to define DLT events and the CTCAE 3.0 Scale will be used for reporting adverse events. The only exceptions relate to defining hematologic DLT events, for this the CTCAE 3.0 Scale will be used, and for capturing veno-occlusive disease (**VOD**), for this the CTCAE 2.0 Scale will be used. (The NCI CTCAE 3.0 and 2.0 can be found at http://ctep.cancer.gov/reporting/ctc.html.) To be evaluable for toxicity, a patient must start treatment and be observed for at least 30 days following the completion of the transplant procedure or have experienced DLT. All patients who are not evaluable for toxicity will be replaced. No dose escalation will occur until DLT evaluations are complete for all patients on a dose level.

As mentioned dose limiting toxicities (DLTs) will be graded according to the modified Bearman Scale. Dose limiting toxicity (DLT) in a given patient is defined as: any grade 3 or 4 toxicity per the modified Bearman Scale (appendix X). Hematologic DLT is defined as: grade 4 neutropenia associated with fever or infection and lasting beyond three weeks, or grade 4 neutropenia lasting for more than 28 days per CTCAE 3.0 toxicity criteria.

The maximum tolerated dose (MTD) is defined as the highest dose tested in which fewer than 33% of patients experienced DLT attributable to the study treatment when at least six patients were treated at the dose and are evaluable for toxicity. The MTD is one dose level below the DLT level. At least six patients will be treated at the MTD. If the MTD does not satisfy these conditions, no expansion at the MTD will occur, as the treatment will be considered lacking adequate safety.

7.2 Dose Escalation Schedule: IMRT

The initial dose level will be 1200 cGy, with dose escalation according to the schedule below.

1. 1200 cGy = 150cGy x 8 doses
2. 1350 cGy = 150cGy x 9 doses
3. 1500 cGy = 150cGy x 10 doses
4. 1750 cGy = 175cGy x 10 doses
5. 2000 cGy = 200cGy x 10 doses

Three patients will be treated at each new dose level. If 0/3 patients experience DLT, 3 patients will be treated at the next dose level. If DLT attributable to the study treatment is experienced in exactly 1/3 patients, 3 more patients (for a total of 6) will be treated at that dose level. If no additional DLT is observed at the expanded dose level (e.g., 1/6 with DLT), the dose will be escalated. Escalation will terminate as soon as two or more patients experience any DLT attributable to the study treatment, at a given dose level. The Phase I trial will be closed when 6 patients have been treated at the next lower dose level, and at most 1/6 patients experience DLT. If more than 1/6 patients experience DLT, the next lower dose will be expanded. There will be no dose escalation within a patient.

The two strata will proceed independently through the dose escalation with the following exceptions: no pediatric patients are to be enrolled on dose level 1 until the adult stratum has been escalated to dose level 2. No pediatric patients will be enrolled to dose level 2 until dose level 2 has been determined to be safe in the adult population, and the same is true for levels 3, 4 & 5.

7.3 Design considerations for a phase II trial.

All patients accrued to the MTD dose level will be included in the response assessment for the phase II portion of the trial.

8.0 STUDY CALENDAR

See appendix V for Study Calendar.

9.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

9.1 Criteria for Evaluation: Acute Myeloid Leukemia (AML) and Myelodysplasia (MDS)

Response and progression will be evaluated in this study using the Revised Recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia [JCO 21:4642-4649, 2003]. The following categories from the Revised Recommendations of the International Working Group will be used:

Morphologic leukemia-free state: Less than 5% blasts in an aspirate sample with marrow spicules and with a count of at least 200 nucleated cells. There are no Auer rods or persistence of extramedullary disease. (The presence of a unique phenotype by flow cytometry identical to what was found in the pre-treatment specimen is viewed as persistence of leukemia.)

Morphologic complete remission (CR): The patient achieves the morphologic leukemia-free state and has an absolute neutrophil count of >1000/uL and a platelet count ≥100,000/uL. The patient is independent of blood transfusions. No duration of response is required to fulfill these criteria.

Cytogenetic complete remission (CRc): Patients who achieve a morphologic CR along with reversion to a normal karyotype by cytogenetic analysis. For patients who have unique markers by routine cytogenetics or by FISH upon enrollment, these markers will be followed on subsequent bone marrow examinations using the same technique(s) to evaluate for CRc.

Molecular complete remission (CRm): Patients who achieve a morphologic CR with no residual disease by molecular or flow cytometic detection methods. For patients with unique multi-dimensional flow cytometry markers at the time of enrollment, these will be repeated on subsequent bone marrow studies to evaluate for CRm.

Morphologic CR with incomplete blood count recovery (Cri): Patient fulfills the criteria for morphologic CR except for residual neutropenia (<1000/uL) and/or thrombocytopenia (<100,000/uL).

Partial Remission (PR): This requires the same hematologic values for a CR but with a decrease of at least 50% in the percentage of blasts to a post-treatment value of 5% to 25% in the bone marrow aspirate. (If the pre-treatment blast percentage was 50-100%, this must decrease to a value between 5-25%. If the pre-treatment blast percentage was 20-49%, this must decrease by at least half to a value greater than 5%.) A value ≤5% is also considered a PR if Auer rods are present.

9.2 Criteria for Evaluation: Chronic Myeloid Leukemia (CML)

Response will be evaluated in this study using the recommendations of the City of Hope CML Disease Committee. The following categories from the Revised Recommendations of the International Working Group will be used:

Morphologic complete remission (CR): The patient must satisfy the following conditions:

a. WBC < 10,000/ul
b. Hemoglobin > 11.0 gm/dl
c. Platelet count < 500,000/ul
d. No immature cells in peripheral blood
e. No palpable splenomegaly

Cytogenetic complete remission (CRc): The patient must have 0% Ph+ metaphases (when a minimum of 20 cells are analyzed) or < 1% by FISH* (minimum of 200 cells analyzed). (Note*: For outside institutions conducting FISH analysis, note background for outside institution.)

Molecular complete remission (CRm): The patient must have no detectable bcr-abl mRNA by RT-PCR.

Morphologic partial remission (PR): The patient must satisfy one or more of the following conditions:

a. WBC > 10,000/ul but < 50,000/ul and 50% below pretreatment values
b. Hemoglobin > 9.0 but < 11.0 gm/dl
c. Platelet Count > 500,000/ul
d. Differential > 1% precursor cells
e. Palpable splenomegaly

9.3 Treatment Failure:

Resistant disease: Patient does not achieve CR or PR upon repeat bone marrow examination after transplant, persistent leukemia in blood or bone marrow.

Aplasia: Patient dies, death occurs while cytopenic with aplastic bone marrow.

Indeterminate cause: Patient dies with no blasts in peripheral blood but no bone marrow examination.

Morphologic relapse: Reappearance of blasts post-CR in peripheral blood or bone marrow.

Molecular or cytogenetic relapse: Reappearance of the molecular or cytogenetic abnormality.

9.4 Endpoint Definitions:

a. Overall survival. Defined as the time from transplant to death due to any cause. If a patient is alive, survival time is censored at the time of last follow-up.

b. Relapse-free survival. Defined as the time from transplant to the first observation of relapsed disease or death due to any cause, whichever occurs first. If the patient has not relapsed or died, relapse-free survival is censored at the time of last follow-up.

c. Event-free survival. Defined as the time from transplant to treatment failure or death due to any cause, whichever occurs first. If the patient has not experienced an event of interest or died, event-free survival is censored at the time of last follow-up

d. Remission duration. Defined as the time from transplant to the first observation of relapsed disease. (Note: Morphologic, molecular and cytogenetic remission duration will be calculated separately.)

10.0 STATISTICAL CONSIDERATIONS

10.1 Phase I

The primary objective of the phase I portion of this study is the determination of the MTD of IMRT when used in conjunction with IV busulfan and VP-16 as a conditioning regimen for allogeneic stem cell transplantation for patients meeting the specified eligibility requirements. The definition of dose limiting toxicity and MTD are given in section 7.1. The number of patients to be treated at each dose level in the phase I trial and the rules for dose escalation are given 7.2. This study is likely to require 18 patients per stratum if the highest dose is well tolerated. It should take approximately 12-18 months to complete this portion of the trial.

The toxicities observed at each dose level will be summarized in terms of type (organ affected or laboratory determination such as absolute neutrophil count), severity (by NCI CTCAE v3.0 and nadir or maximum values for the laboratory measures), date of onset, duration, reversibility, and attribution. Tables will be created to summarize these toxicities and side effects by dose level. Baseline information (e.g., the extent of prior therapy) and demographic information will be presented, as well, to describe the patients treated in this study. All disease responses will be reported. Survival and time to failure will be summarized both by pooling across dose levels and within each dose level, although the primary outcome of the phase II portion will include only patients accrued at the MTD.

10.2 Phase II

An aim of this study is to estimate the efficacy of this regimen in eligible patients. The study is designed to estimate whether 1) the relapse rate and disease-free survival probability at two years is broadly comparable to that obtained with conventional treatment, and 2) to establish whether the more selective radiation targeting yields an improvement in the incidence duration and severity of mucositis. The primary endpoints

will be relapse rate to be estimated for informal comparison to published historical rates, and the fraction of patients experiencing grade 3-5 mucositis. While mucositis grading is subject to variability, 100% of comparable patients receiving previous preparatory regimens involving TBI experience unequivocal high-grade mucositis.

For the adult stratum: the phase II portion will enroll 30 additional patients to the MTD established in the phase I trial, in order to estimate the two-year relapse rate to an accuracy of 18% with 95% confidence (s.e. = 9.1%). If, as hoped, the true (long-run) mucositis rate is better than 70%, there would likely be (e.g., with >95% probability) at least 5 subjects spared high-grade mucositis, which would be a highly significant improvement ($p < 0.002$) compared to historical data (0 out of > 70). Based on the current referral patterns to the City of Hope, it is expected that approximately 6-10 patients per year will be eligible for this study. With a goal of 30 additional patients treated at the MTD, (23 patients already treated) approximately one and a half year of accrual will be required just for the phase II portion.

For the pediatric stratum: the phase II portion will be an exploratory analysis conducted to characterize outcomes for the pediatric population. In addition to the six pediatric cases treated at the 'pediatric' MTD (which may different from the adult population), additional pediatric patients will be enrolled and treated at the MTD, with a maximum of nine additional pediatric patients enrolled during the phase II portion of the study.

10.3 Phase II Monitoring

Early stopping rules are incorporated into the phase II portion of the study for excessive toxicity. However there will be no interim analysis for efficacy during the phase II stage. Toxicities will be recorded using two distinct grading systems; the modified Bearman Scale (Bearman, S., et al, JCO, Vol 6, No 10 (Oct), 1988, pp1562-1568. See appendix X for details.) and the NCI CTCAE 3.0 Scale.

Generally, the modified Bearman Scale will be used to define (grade) 'early stopping' events (toxicities), and the NCI CTCAE 3.0 Scale will be used for reporting adverse events. The only exception relates to how hematologic toxicities are graded and incorporated into the early stopping criteria. For hematologic toxicities the CTCAE 3.0 Scale will be used. The table below will be consulted as relevant toxicities are encountered, so there will be no accrual-based interim analysis point.

Early Stopping Criteria: For each adverse outcome, stop if the cumulative number of patients reaches or exceeds the following limits:

Table of Early Stopping Criteria

# of patients treated at the MTD	# of patients expired due to treatment related causes that would stop the study*	# of patients with grade 3 toxicities that would require an evaluation for safety per Bearman Scale**	Probability that the early stopping rule will be invoked given a failure rate of:		
			10%	15%	20%
12	3	3	0.11	0.26	0.45
18	5	5	0.12	0.27	0.47
24	6	6	0.12	0.31	0.53
30	8	8	0.13	0.31	0.53

36	9	9	0.13	0.32	0.55

* Note: The stopping rules are not statistically based; expected treatment related mortality should not to exceed 25%.
** Note: For hematologic toxicities: Any grade 4 neutropenia associated with fever or infection and lasting beyond three weeks, or grade 4 neutropenia lasting for more than 28 days per CTCAE 3.0 toxicity criteria should be counted toward the early stopping rule.

Any patient who receives treatment as part of the phase II portion of this protocol will be evaluable for toxicity. Each patient will be assessed periodically according to the treatment schedule for the development of any toxicity. The toxicity rule for safety will be assessed as each patient reaches day +30 post transplantation. If more than the specified number of patients (noted in the table above) have significant treatment related toxicities, then the safety of the study will be evaluated.

10.4 Analysis of Clinical Endpoints

There will be one combined statistical analysis for efficacy. In accordance with the primary study objectives, we will perform descriptive statistical analyses on these data after the phase II study is complete. Our primary endpoints will be OS, RFS, EFS, TRM, and RR with infection and acute- chronic- GVHD as secondary endpoints. Confidence Intervals will be estimated by calculating exact 95% confidence limits for a binomial parameter. The time-to-event endpoints, such as RFS and OS, will be estimated using the product limit method of Kaplan-Meier and tested using the Log-Rank test.

11.0 REGISTRATION GUIDELINES

Once a signed informed consent has been obtained and all pre-treatment evaluations have been performed, patients will be entered on study after review of patient eligibility criteria by the assigned Clinical Research Associate from the City of Hope Department of Biostatistics. Patients may be screened for registration by calling the Department of Biostatistics at extension 62468.

12.0 RECORDS TO BE KEPT AND DATA SUBMISSION SCHEDULE

12.1 Confidentiality of Records:

The original data collection forms will be stored in secured cabinets in the Department of Biostatistics.

12.2 Patient Consent Form:

At the time of registration, three signed and dated copies of the patient Informed Consent form with the Human Rights must be available (for patient, patient's medical chart, and one for the City of Hope Biostatistics Office).

13.0 WOMEN AND MINORITIES GUIDELINES

All eligible patients from both genders and from all racial/ethnic groups will be recruited equally into this trial, with the only exclusionary criteria being those stated in Section 5.0. Based on our patient populations and previous experience with BMT for advanced hematological malignancies, the anticipated rates of entry into this study by gender and race/ethnicity are as follows:

Race/Ethnicity by Gender for Advanced Malignancy Patients Receiving HSCT at City of Hope

	American Indian or Alaskan Native	Asian or Pacific Islander	Black, not of Hispanic Origin	Hispanic	White, not of Hispanic Origin	Other or unknown
Female	0%	8%	1%	32%	58%	1%
Male	<1%	8%	3%	33%	54%	3%
Total	<1%	8%	2%	33%	55%	2%

14.0 DATA MANAGEMENT

The assigned Clinical Research Associate from the Department of Biostatistics will maintain all primary data, including eligibility checklist, pre-study and initial data forms, consolidation, transplant data, pathology reports and off-study information. Data will be collected by the CRA at the time of each patient evaluation. Records will be stored in a secure location within the Biostatistics Department. See Study Calendar and Appendix XI for time points for grading toxicities.

15.0 ETHICAL AND REGULATORY CONSIDERATIONS

This study is to be approved by the Institutional Review Board (IRB) according to City of Hope ethical and regulatory guidelines. All patients will have signed an informed consent for participation in research activities, and will have been given a copy of the Experimental Subject's Bill of Rights.

When results of this study are reported in medical journals or at meetings, identification of those taking part in this study will be withheld. The medical records of subjects will be maintained in strictest confidence, according to current legal requirements. However, these records will be made available for review, as required by the Food and Drug Administration (FDA) or other authorized users such as the National Cancer Institute (NCI), under the guidelines established by the Federal Privacy Act.

16.0 DATA AND SAFETY MONITORING PLAN

A. Definition of Risk Level

This is a risk level 4 study as defined in the Guidance Policy and Procedures for Data and Safety Monitoring for In-House trials at City of Hope. http://www.infosci.coh.org/gcrc/doc/dsmp.doc This study involves tissue transplant and chemotherapy.

B. Monitoring and Personnel Responsible for Monitoring

The Protocol Management Team (PMT) consisting of the PI, Collaborating Investigator(s), CRA/protocol nurse and statistician are responsible for monitoring the data and safety of this study, including implementation of the stopping rules for safety and efficacy, including implementation of the stopping rules for safety and efficacy (see section 10.3).

For phase I of the trial, monitoring by the PMT will be done using the phase I tracking log, the objective will be to monitor data and safety for dose escalation. Data and safety will be reported to the City of Hope DSMB after each dose level, and the PMT will decide before patients are enrolled on the phase II portion of the trial.

For phase II of the trial, data and safety will be reported to the City of Hope DSMB annually. In addition to the annual report, any early evaluations for safety and/or treatment related mortality will also be reported as these assessments are made (per guidelines set in section 10.3 and 10.4 of the protocol). This report (the PMT report) will include a summary of accrual, adverse events and treatment related mortality.

C. Adverse Events

The frequency for the recording of toxicities are outlined in Appendix V and Appendix X.

C.1. Reporting

Adverse events must be reported to the City of Hope DSMB and IRB according to definitions and guidelines at http://www.infosci.coh.org/gcrc/doc/dsmp.doc and http://resadmin.coh.org/doc/irb3810.doc which are defined below. SAE's will be monitored by the PMT. Less than serious adverse events will be reported only at the time of protocol continuation reports. All AE's occurring during the study will be recorded in the CRF. Grade 3, 4 toxicity will be reported to the IRB except Grade 3, 4 laboratory abnormalities which will be reported only if clinically significant.

C.2. Adverse Event

An adverse event (AE) is any untoward medical experience or change of an existing condition that occurs during or after treatment, whether or not it is considered to be related to the protocol intervention. All AEs occurring during this study, whether observed by the physician, nurse, or reported by the patient, will be recorded on the City of Hope National Medical Center Adverse Events (CTCAE version 3.0) form.

C.3. Serious Adverse Event

A serious adverse event (SAE) is defined as *any expected or unexpected adverse event* (AE, generally equivalent to CTCAE grades 3, 4 or 5) that is *related or unrelated* to the intervention that results in any of the following outcomes:

- Death
- A life-threatening event
- In-patient hospitalization (not required as part of the treatment) or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Causes cancer
- Is an overdose

Certain medical events that may not result in death, be life-threatening, or require hospitalization, may also be considered a serious adverse event when appropriate medical or surgical intervention is necessary to prevent one of the outcomes listed above.

C.4. Unexpected Adverse Event

Any event in which the severity or specificity is not consistent with the risk information described in the protocol, and the event is not anticipated from the subject's disease history or status.

C.5. Expected Adverse Event

Any event in which the severity or specificity is consistent with the risk information described in the protocol or is anticipated based on the subject's medical history.

C.6. Attribution

For reporting purposes, attribution is the assessment of the likelihood that an AE is caused by the research agent or protocol intervention. The attribution is assigned by the Principal Investigator after considering the clinical information, the medical history of the subject, and past experience with the research agent/intervention. This is recorded using the Adverse Event Report (COH AER) form (http://resadmin.coh.org/doc/irb3820.doc) in one of 5 categories scored as the following: 5=related, 4=probably related, 3=possibly related, 2=unlikely related and 1=unrelated. The attribution is subject to change as follow-up information becomes available, and it can be changed by the DSMB or by the IRB in the process of review.

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APPENDIX I

IV BUSULFAN KINETICS FORM

IRB#: _____ DATE: _____ (CIRCLE WEIGHT USED)

PATIENT _____ DOSE #_____ Actual Body Weight _____

Medical Record #_____ Start time: _____ Ideal Body Weight _____

MD/Pager # _____ Stop Time: _____ Adjusted IBW _____

Coordinator/Pager #_____ DOSE: _____mg

INFUSION TO RUN OVER 2 HOURS

Tube #	Collection Schedule	Proposed Collection Time	Actual Collection Time
1	Immediately prior to beginning of infusion	APPROX. 0555	
2	Immediately prior to end of infusion	APPROX. 0755	
3	15 minutes post infusion	APPROX. 0815	
4	30 minutes post infusion	APPROX. 0830	
5	60 minutes post infusion (1 hour)	APPROX. 0900	
6	180 minutes post infusion (3 hours)	APPROX. 1100	
7	240 minutes post infusion (4 hours)	APPROX. 1200	

** ALL samples to be obtained in 7cc green top tubes (Sodium Heparin) and kept on ice at Nurses Station.

Then send to Clinical Pathology.

RN SIGNATURE _____

Appendix II

TREATMENT SCHEMA FOR DONORS

1). G-CSF Administration to Donors: All donors will receive G-CSF 10 µg/kg/day for 6 consecutive days from day –5 to day 0. G-CSF will be administered by a subcutaneous injection daily beginning 5 days prior to day 0 (defined as the day marrow would ordinarily be given).

2). PBSC Collection: Donors may undergo vein to vein collections or may receive an appropriate catheter inserted on or before day of the treatment regimen. Donors will receive -5 daily doses of G-CSF, 10µg/kg/day by subcutaneous injection commencing on day –5. These doses will be administered each day in the Outpatient Department or at home.

Treatment Schema for Donor

Days	**-5**	**-4**	**-3**	**-2**	**-1**	**0**
G-CSF 10µg/kg/SQ	X	X	X	X	X	
PBSC Collection					X	X

PBSC's will be collected in the afternoon of day -1 and reinfused on day 0. *If the collection on day -1 contains less than 5.0 x 10^6 CD34+ cells per kg recipient weight, a second collection will be performed the following morning and transfused on day 0.

If PBSC's cannot be collected by a vein to vein technique, a percutaneous Mahurkar catheter will be inserted.

General procedures will include the use of a standard apheresis machined (COBE Spectra, Lakewood Colo.), and processing up to 16 l of whole blood during the collection. (Refer to Standard Practice Manual for collection procedure).

3. Bone Marrow collection: Donors may undergo bone marrow collection in lieu of PBSC's. Bone marrow collection will be done per current Hematopoietic Cell transplant Program Clinical Manual of Standard Operating Procedures (Section B.004).

APPENDIX III

ACUTE GRAFT VERSUS HOST DISEASE STAGING AND GRADING

See current Hematopoietic Cell Transplant Program Clinical Manual of Standard Operating Procedures

Standardized Grading of Acute and Chronic GVHD
G.003.01

APPENDIX IV

GRADING OF CHRONIC GRAFT VERSUS HOST DISEASE

See current Hematopoietic Cell Transplant Program Clinical Manual of Standard Operating Procedures

Management of Chronic Graft vs Host Disease
G.004.01

STUDY CALENDAR

HD Therapy/Transplant therapy (All testing (except BM bx 4 weeks) has to be completed no more than 28 days prior to starting treatment)

Required studies	Pre admit	Day -19	Day -15	Day -14	Day -13	Day -12	Day -11	Day -10	Day -9	Day -8	Day -7	Day -6	Day -5	Day –4	Day -3	Day -2	Day -1	Day 0	Day 1	Day 2	Day 3	Day 4	Day 30*	Day 100*	Day 180**	Yearly X 2 yrs**
Week Day		Th	M	T	W	Th	F	Sa	Su	M	T	W	Th	F	Sa	Su	M	T	W	Th	F	Sa	-	-	-	-
CBC, Diff, PLT [2, 3]	X		X		X		X			X		X		X			X	X	X	X	X	X		X	X	X
BMP[4]	X			X		X		X			X		X		X			X		X		X				
CMP [1]	X		X		X		X			X		X		X			X		X		X		X	X	X	X
MG, uric acid [1]	X		X		X		X			X		X		X			X		X		X		X	X	X	X
LDH, phosphorus [1]	X		X		X		X			X		X		X			X		X		X		X	X	X	X
Hepatitis A,B,C	X																									
HIV [9]	X																									
PT, PTT [9]	X																									
UA	X																									
24hr CLcr	X																									
Pregnancy test	X																									
CMV, HSV/HZV [9]	X																									
Immuno-globulin [9]	X																									
PFT [9]	X																						X	X	X	X
EKG [9]	X																									
CXR [7, 9]	X																									
CT Scan Chest, ABD [9]	X																									
ECHO or MUGA [9]	X																							X		
LP/MTX see 6.1.G	X																									
BM asp, bx, cytogenetics	X																						X	X		X
Dilantin level					X																					
Busulfan levels			**XX**		**XX**[8]																					
TREATMENT																										
Dilantin [10]		X	X	X	X	X	X	X	X	X	X	X														
Busulfan						X	X	X	X																	
IMRT										X	X	X	X													
VP-16															X											
PSC's or BM																		X								
CNS Disease patients - see section 6.1.G																										
TOXICITY																										
Toxicity Monitoring					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[1] Every Monday, Wednesday, Friday during hospitalization or as clinically indicated

[2] CBC and platelets done daily during hospitalization

[3] Diff. should be done daily until no blasts are present in peripheral blood then started again when WBCs ≥ 500 until ANC >500 for 3 consecutive days and then on Mondays, Wednesdays and Fridays until discharge

[4] Basic Metabolic Panel (Sodium, Potassium, Chloride, Carbon Dioxide, Blood Urea Nitrogen, Creatinine, Glucose, Calcium)

[6] Comprehensive Metabolic Panel (Sodium, Potassium, Chloride, Carbon Dioxide, Calcium, Urea Nitrogen, Creatinine, Glucose, Albumin, Bilirubin Total, Alk Phos, Total Protein, SGPT, SGOT) with magnesium, uric acid, LDH & phosphorous

XX blood sample shipment

[7] CXR to be done weekly until day 30

[8] If required

[9] Tests are good for 3 months if transplant delayed for non-medical reason.

[10] Dilantin will be given daily consecutively until day –6 or day after last busulfan dose

* Day 30 through Day 100 tests evaluations are +/- 7 working days

** Evaluations post Day 100 are +/- 14 days

APPENDIX VI

COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (VERSION 3.0 & 2.0)

A copy of CTCAE version 3.0 and 2.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/reporting/ctc.html

APPENDIX VII

GUIDELINES FOR REPORTING ADVERSE EVENTS

City of Hope Adverse Event Reporting guideline can be found at:
http://resadmin.coh.org/doc/irb3810.doc

APPENDIX VIII

ELIGIBILITY CHECKLIST

Inclusion Criteria			
The answers to the following criteria must all be marked YES.			
1	____Yes	____No	Does the patients have documented acute myeloid leukemia not in first remission or second remission i.e. after failing remission induction therapy or in relapse or beyond second remission? **OR** Does the patients have chronic myeloid leukemia in blastic phase of the disease? NOTE: Patients with refractory anemia with excess blasts and in transformation will be eligible.
2	____Yes	____No	Does the subject have a HLA (A, B, C, DR) identical sibling or fully-matched unrelated donor who is willing to donate bone marrow or primed blood stem cells? NOTE: All ABO blood group combinations of the donor/recipient are acceptable since even major ABO compatibilities can be dealt with by various techniques. (Red cell exchange or plasma exchange).
3	____Yes	____No	Has the patient had prior therapy? NOTE: Prior therapy with VP-16 and busulfan is allowed.
4	____Yes	____No	Patient must have reached their 6th birthday and must not have passed their 55th birthday. Age_____
5	____Yes	____No	Does the subject have an ejection fracture of greater than or equal to 50% by MUGA or echocardiogram? (Either method for measuring cardiac function is acceptable, however, the same scan must be used throughout treatment and follow-up to monitor the patient for cardiac toxicity.) Ejection fracture_____ Date Obtained_____
6	____Yes	____No	Has the subject had an electrocardiogram? Date Obtained_____
7	____Yes	____No	Does the patients have a serum creatinine of less than or equal to 1.2 or creatinine clearance > 80ml/min? Serum Creatinine_____ IULN_____ Date obtained_____

			Creatinine Clearance (estimated or measured – circle one)_____ Date obtained_____
8	____Yes	____No	Does the patient have a bilirubin of less than or equal to 1.5? Bilirubin_____ Date obtained_____
9			Does the patient have a SGOT and SGPT less than 5 times the upper limit of normal. SGOT_____ ULN_____ Date obtained_____ SGPT_____ ULN_____ Date obtained_____
10	____Yes	____No	Does the patient have $FEV_1$and DLCO greater than 50% of predicted normal value based on Pulmonary function tests? FEV1_____ Predicted Normal Value_____ DLCO_____ Predicted Normal Value_____ Date obtained_____
11	____Yes	____No	Is the time from the end of last induction or reinduction attempt greater than or equal to 21 days? End Date of treatment_____
12	____Yes	____No	Has the patient signed the informed consent form approved by the IRB? Date informed consent form signed_____ NOTE: The patient, family member and transplant staff physician (physician, nurse, and social worker) meet at least once prior to starting the transplant procedure. During this meeting all pertinent information with respect to risks and benefits to donor and recipient will be presented. Alternative treatment modalities will be discussed. The risks are explained in detail on the enclosed consent forms.
Exclusion Criteria			
The answers to the following criteria must all be marked NO.			
1	____Yes	____No	Has the patient had prior radiation therapy that will exclude the

			use of total body irradiation?
2	____Yes	____No	Has the patients undergone a previous bone marrow transplantation and relapsed?
3			Does the patient have a psychological or medical condition that the physician deems unacceptable to proceed to allogeneic bone marrow transplant?
4	____Yes	____No	Is the patient currently pregnant or nursing? Patient must not be pregnant or nursing because of the teratogenic potential of the drugs/radiation in this study. Women/men of reproductive potential must have agreed to use an effective contraceptive method.

Appendix IX: Modified Bearman Scale

	Grade I	Grade II	Grade III
Cardiac toxicity	*Mild EKG abnormality, not requiring medical intervention; or noted heart enlargement on chest x-ray with no clinical symptoms*	*Moderate EKG abnormalities requiring and responding to medical intervention; or requiring continuous monitoring without treatment; or congestiveheart failure responsive to digitalis or diuretics*	*Severe EKG abnormalities with no or only partial response to medical intervention; or heart failure with no or only minor response to medical intervention; or decrease in voltage by more than 50%*
Bladder toxicity	*Macroscopic hematuria after 2 days from last chemotherapy dose with no subjective symptoms of cystitis and not caused by infection*	*Macroscopic hematuria after 7 days from last chemotherapy dose not caused by infection; or hematuria after 2 days with subjective symptoms of cystitis not caused by infection*	*Hemorrhagic cystitis with frank blood, necessitating invasive local intervention with installation of sclerosing agents, nephrostomy or other surgical procedure*
Renal toxicity	*Increase in creatinine up to twice the baseline value (usually the last recorded before start of conditioning)*	*Increase in creatinine above twice baseline but not requiring dialysis*	*Requirement of dialysis*
Pulmonary toxicity	*Dyspnea without chest x-ray changes not caused by infection or congestive heart failure; or chest x-ray showing isolated infiltrate or mild interstitial changes without symptoms not caused by infection or congestive heart failure*	*Chest x-ray with extensive localized infiltrate or moderate interstitial changes combined with dyspnea and not caused by infection or CHF; or decrease of PO2 (> 10% from baseline) but not requiring mechanical ventilation or > 50% O2 on mask and not caused by infection or CHF*	*Interstitial changes requiring mechanical ventilatory support or > 50% oxygen on mask and not caused by infection or CHF*
Hepatic toxicity	*Mild hepatic dysfunction with bilirubin ≥ 2.0 mg/dL and ≤ 6.0 mg/dL or weight gain > 2.5% and < 5% from baseline, of non-cardiac origin; or SGOT increase more than 2-fold but less than 5-fold from lowest preconditioning*	*Moderate hepatic dysfunction with bilirubin > 6.0 mg/dL and < 20 mg/dL; or SGOT increase > 5-fold from preconditioning; or clinical ascitis or image documented ascitis > 100 mL; or weight gain > 5% from baseline of non-cardiac origin*	*Severe hepatic dysfunction with bilirubin > 20 mg/dL; or hepatic encephalopathy; or ascitis compromising respiratory function*
CNS toxicity	*Somnolence but the patient is easily arousable and oriented after arousal*	*Somnolence with confusion after arousal; or other new objective CNS symptoms with no loss of consciousness not more easily explained by other medication, bleeding or CNS infection*	*Seizures or coma not explained (documented) by other medication, CNS infection, or bleeding*
Stomatitis	*Pain and/or ulceration not requiring a continuous IV narcotic drug*	*Pain and/or ulceration requiring a continuous IV narcotic drug (morphine drip)*	*Severe ulceration and/or mucositis requiring preventive intubation; or resulting in documented aspiration pneumonia with or without intubation*
GI toxicity	*Watery stools > 500 mL but < 2,000 mL every day not related to infection*	*Watery stools > 2,000 mL every day not related to infection; or macroscopic hemorrhagic stools with no effect on cardiovascular status not caused by infection; or subileus not related to infection*	*Ileus requiring nasogastric suction and/or surgery and not related to infection; or hemorrhagic enterocolitis affecting cardiovascular status and requiring transfusion*

APPENDIX X

TIME POINTS TO GRADE TOXICITIES AND COLLECT DATA

1. 30 days post PBSCT/BMT

   Complete Common Toxicity Criteria (CTC) Form

2. 31 to 100 days post PBSCT/BMT

   Complete Common Toxicity Criteria (CTC) Form every month

   Complete allogeneic transplant and disease specific forms

3. Day 101 – 365 post transplant

   Complete long-term follow-up form

4. Yearly for two years

   Complete long-term follow-up form

APPENDIX XI

PARAMETERS FOR TARGETED TBI

Phase I - II Study of IV Busulfan and Etoposide (VP16) Combined with Escalated Doses of Large field Image-guided Intensity Modulated Radiation Therapy (IMRT) using Helical Tomotherapy as a Preparative Regimen for Allogeneic Hematopoietic Stem Cell (HSC) Transplantation for Patients with Advanced Myeloid Malignancies

TARGET STRUCTURES WITH DOSE ESCALATION

Skeletal Bone: C, T and L spine, clavicles, scapula, pelvis, sacrum, all bones of the bilateral upper and lower extremities.

Major Lymph Node Chains: cervical, supraclavicular, axillary, mediastinal, para-aortic, pelvic, inguinal-femoral

Testes

TARGET STRUCTURES KEPT AT 1200 cGy (NO DOSE ESCALATION)

Spleen and splenic-hilar nodes
Liver and porta-hepatic nodes
Ribs
Sternum
Brain and skull

NON-TARGET STRUCTURES

Scalp
Orbits
Lens
Thyroid
Oral Cavity
Mandible
Parotids
Larynx/Hypopharynx
Esophagus
Lungs
Heart
Breasts
Kidneys
Stomach
Small and Large Intestine
Rectum
Bladder

TARGET DOSE, FRACTION SIZE, SCHEDULE AND DOSE ESCALATION SCHEME

Initial Dose Level: 1200 cGy
Fraction and Schedule: 150 cGy QD or BID (minimum 6 hours between fractions)
Dose Escalation Scheme:

Level	Fraction and Schedule	Total Dose
1	150 cGy BID x Days 1-4	1200 cGy
2	150 cGy BID Day 1 -4 then 150 cGy QD Day 5	1350 cGy
3	150 cGy BID Days 1-5	1500 cGy
4	175 cGy BID Days 1-5	1750 cGy
5	200 cGy BID Days 1-5	2000 cGy