UNIVERSITY OF MINNESOTA BONE MARROW TRANSPLANTATION PROGRAM

AUTOLOGOUS PERIPHERAL BLOOD STEM CELL TRANSPLANT FOR ACUTE NON-LYMPHOCYTIC LEUKEMIA (AML)

MT2006-13

October 31, 2018

Study Committee
Daniel Weisdorf, M.D.,Chair
Paul J. Orchard, M.D., Co-Chair
John Wagner, M.D.
Claudio Brunstein, M.D.
Jeffrey Miller, M.D.
Kathryn Dusenbery, M.D.
Todd DeFor, M.S.

PROTOCOL CHANGES

DATE	PROTOCOL CHANGE	IRB APPROVAL
7/11/2008	revised the eligiblity to exclude patients with active or resistant CNS leukemia; not those with prior CNS leukemia	
2/13/2009	Corrected typo in section 4.2.2	
12/04/2013	Corrected typo in section 4.3.2; adjustment to listed busulfan dose, section 4.3.2	
8/4/2016	Updated to current standard of care guidelines: -follow up will be two years post BMT (subjects then transferred to BMT database follow up) -updated data and safety monitoring plan -updated required observations table -updated TBI guidelines Removed Linda Burns from study committee	
10/31/2018	Removed 1.5 year visit from observations table; updated link to Masonic Cancer Center's Data & Safety Monitoring Plan	

TABLE OF CONTENTS

Schema MT 2006-13
Autologous AML

Chemotherapy Priming :
Cytoxan 4 Gm/m^2 IV day 0
Etoposide 300 mg/m^2 day 0
Etoposide 300 mg/m^2 day +1
Dexamethasone 20 mg/m^2 bid day 0
Dexamethasone 20 mg/m^2 bid day +1

G-CSF 10 ug/kg/day - Begin day +3

Autologous Stem Cell Collection
(when counts recover)

BMT Admission **2 years to 70 years**		**BMT Admission** **Patients < 2 years of age** **OR** **Any patient who cannot receive TBI**	
Day -7	TBI 165 cGy/dose BID	Day -7	Busulfan .8 mg/kg IV q 6 hr
Day -6	TBI 165 cGy/dose BID	Day -6	Busulfan .8 mg/kg IV q 6 hr
Day -5	TBI 165 cGy/dose BID	Day -5	Busulfan .8 mg/kg IV q 6 hr
Day -4	TBI 165 cGy/dose BID	Day -4	Busulfan .8 mg/kg IV q 6 hr
Day -3	Cytoxan 60 mg/kg IV	Day -3	Cytoxan 60 mg/kg IV
Day -2	Cytoxan 60 mg/kg IV	Day -2	Cytoxan 60 mg/kg IV
Day -1		Day -1	
Day 0	Stem Cell Infusion	Day 0	Stem Cell Infusion
Day +1	G-CSF	Day +1	G-CSF

1.0 OBJECTIVES

In order to improve clinical outcomes and reduce the morbidity of bone marrow transplantation for patients with acute non-lymphocytic leukemia (AML), this study is designed to assess:

1.1 Can sufficient peripheral blood stem cells (PBSC) be collected from subjects with AML using cyclophosphamide (Cy), etoposide (VP-16) and granulocyte-colony stimulating factor (G-CSF) mobilization?

1.2 What is the rate of myeloid, platelet and erythroid recovery following autologous PBSC transplant?

1.3 What is the disease free survival (DFS) rate of patients with AML receiving PBSC auto grafts?

2.0 BACKGROUND AND RATIONALE

2.1 Chemotherapy and Allogeneic BMT for AML:
With current induction regimens using combinations of cytosine arabinoside (Ara-C) and daunorubicin the majority of patients with acute non-lymphocytic leukemia will achieve remission; however, the majority of these patients relapse. The 5 year disease free survival (DFS) with chemotherapy is approximately 30% in adults, but may be somewhat higher in children treated on current very aggressive chemotherapy regimens (1,2). Patients who receive intensive cytoreductive therapy followed by allogeneic bone marrow transplantation (BMT) using matched related donors have 5 year DFS rates of approximately 50-60% (3-6).

2.2 Autologous BMT for AML:
Autologous marrow transplantation has been an accepted form of treatment for AML when a matched related donor is not available, or for certain ANLL subgroups. While the rate of relapse is higher with autologous BMT for AML than allogeneic transplant, in several comparative reports due to the increased transplant related mortality of allogeneic BMT the long term disease free survival rates are comparable (1,7). Studies have consistently documented 5 year disease-free survival (DFS) rates of 40-50% for patients in first remission (1,8). The survival of patients in second remission or in those transplanted in relapse are lower (9-11). The difficulties related to achieving long term DFS with autologous BMT include:

2.2.1 BMT Related Toxicity:
There is a 10-15% peri-BMT mortality observed with autologous transplantation for AML (6,12). Modfications that would decrease the period of neutropenia would be beneficial. In this context, the use of peripheral blood stem cells as a source of CD34+ cells has been explored to obtain more rapid engraftment (13-15).

2.2.2 Relapse:
The largest obstacle to prolonged DFS following autologous BMT for AML is relapse, occurring in 30-40% of patients. Relapse may result from residual disease in the marrow, as

has been documented by molecular techniques (13), or from incomplete eradication of disease *in vivo*. While purging with agents such as 4-hydroxycyclophosphamide (4-HC) has been used to decrease the rate of relapse (16,17), currently this agent is not available for clinical trials. In addition, engraftment may be delayed following purging, and may therefore lead to increased morbidity and mortality (18). It is possible that the chemotherapy used in this study prior to the collection of peripheral blood stem cells will improve disease free survival.

2.3 Autologous Transplant in "Good Risk" AML Patients:

Recent studies relating to the prognosis of patients with AML based on chromosomal findings have suggested that it may be possible to identify a patient population where this is likely to have an improved outcome (24,25). Specifically, patients with t8:21 and inv16 have been reported to have a 5 year DFS rate of approximately 60% or higher, especially if high dose cytosine arabinoside is used in the consolidation regimen (24). Based on this information, it is important to address the issue of whether these patients should be offered autologous transplantation in first remission. A randomized study of autologous transplantation or no further therapy in patients with AML in first remission was recently reported (26), suggesting that autologous transplantation was superior on an intent to treat analysis for providing DFS at 7 years (53 vs. 40%; p=0.04). In addition, when patients in a "good risk" category were identified, those that underwent autologous transplantation had a decreased risk of relapse (25% vs. 49%, p=0.02) as well as improved DFS (70% vs. 48%, p=0.04).

2.4 The Use of Peripheral Stem Cells (PBSC) in BMT:

It has been well documented that CD34+ cells can be identified in the peripheral blood, and that the proportion of these early progenitors can be increased using cytokines such as granulocyte-colony stimulating factor (G-CSF) and/or chemotherapy (14,18). In autologous BMT using PBSC as a source of CD34+ cells rapid hematopoietic recovery has been observed, making this approach attractive as an alternative to harvesting autologous marrow (31). Unfortunately, in patients heavily pre-treated with chemotherapy it may prove more difficult to obtain adequate numbers of peripheral blood CD34+ cells. For AML patients receiving autologous peripheral blood stem cell transplants, it has been shown that increasing the cell dose decreases the mortality observed by day 100 (14,32). The recovery of the platelet count following autologous BMT for AML has also been of concern (14,33). For these reasons, we will administer $\geq 2.5 \times 10^6$ CD34+ cells/kg to patients on this study.

2.5 Chemotherapy and G-CSF Priming of PBMC for AML.

The administration of G-CSF increases the number of circulating CD34+ cells that can be obtained from the peripheral blood. Alternatively, chemotherapeutic agents have been used in this capacity, with or without G-CSF. Due to concerns regarding the potential stimulation of myeloid leukemia by priming with G-CSF (14,21), in this investigation we will combine G-CSF with chemotherapeutic agents in an attempt to decrease concern regarding possible risk of leukemic stimulation. An agent commonly used in this role is Cy, which has often been administered in a single dose of 4 gm/M^2. It has been suggested that the combination of Cy (4 gm/M^2 IV x 1) and VP-16 (200 mg/M^2 IV x 3) may increase the CD34+ cell yield compared to Cy alone (34). As VP-16 has substantial activity against AML, Cy and VP-16 followed by G-CSF (10 μg/kg/day subcutaneously [SC]) will be used prior to PBSC harvest for mobilization. This dose of G-CSF was chosen as it appears that the combination of Cy, VP-

16 and doses of G-CSF of at least 10 μg/kg/day were associated with increased yield of CD34+ cells and faster hematopoietic recovery (35).

3.0 ELIGIBILITY AND EXCLUSION CRITERIA

Children under the age of two are eligible for this protocol, but will not receive total body irradiation. Instead, children under the age of two will receive Bu/Cy conditioning as the preparative regimen in order to obviate deleterious effects of radiation at this age. Patients who cannot receive TBI (for example those with prior radiation therapy) will also receive the Bu/CY conditioning.

3.1 AML

All children and adults less than the age of 70 with AML who have achieved a first or second bone marrow remission are eligible for this protocol. Patients must undergo peripheral blood stem cell collection or marrow harvest while in remission and must not be expected to have better outcomes with allogeneic transplantation.

Patients with cytogenetic abnormalities suggesting an improved prognosis [t(8:21), t(15;17) and inv(16)] will be eligible for transplantation in first remission.

3.2 Allogeneic transplant with an HLA-identical sibling will be recommended for patients <55 years. If the patient refuses allogeneic transplant, they may still be eligible for this protocol.

3.3 Patients can also be deemed not eligible for transplant because of specific organ toxicity. Specifically, patients with pre-existing compromise to the heart, lungs, kidney, CNS or liver may be excluded:

3.3.1 ECOG (See Appendix II).
Performance status: 0 or 1

3.3.2 Heart
The patient must be free of symptoms of uncontrolled cardiac disease, and must not have compromised cardiac function detected by ECHO or by gated cardiac blood flow scan (MUGA) LVEF >45%).

3.3.3 Kidney
The patient must have a corrected creatinine clearance ≥50% of normal.

3.3.4 Liver
The total serum bilirubin ≤ 2.5 mg/dL; ALT <2 x upper limit of normal.

3.3.5 Lung
Patients must have no significant obstructive airways disease or resting hypoxemia (PO_2 <80), and must have acceptable diffusion capacity (DLCO > 50% of predicted).

3.3.6 Central Nervous System:
Patients must be free of active or ongoing ischemic or degenerative CNS disease and no active or resistant CNS leukemia.

4.0 TREATMENT SCHEMA

4.1 Peripheral Blood Stem Cell Mobilization, Collection:

4.1.1 Criteria to Begin Priming for PBSC:
Prior to proceeding with an autologous stem cell collection, a remission must be achieved (M1 marrow; less than 5% blasts in a marrow which is slightly hypocellular, normocellular or hypercellular), and the patient must have recovered blood counts (absolute neutrophil count >1500 cells/mL, Hgb (untransfused) >9 gm/dL, platelet count (untransfused) >100,000 cells/mL); all unsupported by hematopoietic growth factors for ≥14 days. Patients should be at least 4 weeks from previous myelosuppressive chemotherapy. Cytogenetic complete remission is necessary to be eligible for peripheral stem cell or marrow harvest.

4.1.2 Priming for PBSC Collection
Patients will receive chemotherapy and G-CSF priming as follows:

Admit to hospital:

After > 4 hours of hydration (rate of 3000 mL/M^2/day)

1. **Cyclophosphamide (Cy)** 4 gm/M^2 x 1 (day 0)
   Mesna 800 mg/M^2 x 5 doses; (to begin 10-15 min. before Cy, at 1 hr, 3, 6 and 12 hrs.)

2. **Dexamethasone** 20mg/m^2 x 4 doses q 12 hr given IV push pre cytoxan on day 0 and then q 12h.

3. **Etoposide (VP-16)** 300 mg/M^2/day x 2 days (day 0-1)
   VP-16 is to be given over 3 hours IV.

4. **G-CSF** (subcutaneously; SC 10 μg/kg/day* from day +3 until apheresis is completed
   *Round dose to G-CSF vial size;

4.1.3 Apheresis will be performed when the ANC achieves 1000 cells/mL, and will continue for a minimum of 4 daily planned collections.

4.1.4 The minimum CD34+ cell dose is >2.5 x 10^6 cells/kg. If this cell dose is not achieved at the end of 4 collections, 2 additional collections can be performed; (total of 6 collections).

4.1.5 Should the total number of CD34+ cells from 6 collections be inadequate to obtain the minimum cell dose (2.5 x 10^6 CD34+ cells/kg), a bone marrow harvest will be planned. A bone marrow examination will be performed, including a biopsy and aspirate, at the termination of the PBSC collection to confirm remission. If remission is confirmed, and if the peripheral counts and marrow cellularity are sufficient (see

Section 4.1.1), the patient will remain off G-CSF for 7 days. GM-CSF (250 ug/M^2/day) will then be started for 5 days to increase the marrow cellularity, after which a bone marrow harvest will be performed on day 6. A total of 1.5 liters of marrow will be drawn from adult patients, or if the patient is ≥60 kg. For children and those <60 kg, 20 mL/kg of marrow will be obtained during a harvest.

4.2 Bone Marrow Harvest Without Prior PBSC Collections:

4.2.1 Children <10 kg will not be eligible for PBSC collection, and will undergo a primed bone marrow harvest using GM-CSF. Other patients that are unable to have PBSC collections performed may proceed with a bone marrow harvest at the discretion of the protocol chairperson.

4.2.2 Patients to undergo a marrow harvest without prior PBSC collections will receive 5 days of GM-CSF (250 mcg/M^2/day) IV or SC prior to harvest to increase cellularity and marrow will be harvested on day 6. Marrow and blood specimens will still be obtained with the initial bone marrow evaluation and at the time of harvest if a cytogenetic abnormality was previously described. A dose of 20 mL/kg of marrow will be obtained during the harvest.

4.3 Transplant Schema

4.3.1 Patients over the age of two will receive a cytoreductive regimen of "TBI/CY". A fluid flush of 3000 mL/M^2 is to begin 10 hours prior to the infusion of Cy (Section 4.6.3), with administration of MESNA to total 120 mg/kg according to current guidelines.

Day	Agents
-7	TBI 165 cGy /dose given twice a day*
-6	TBI 165 cGy /dose given twice a day
-5	TBI 165 cGy /dose given twice a day
-4	TBI 165 cGy /dose given twice a day
-3	Cyclophosphamide 60 mg/kg IV over 2 hrs (10 AM)
-2	Cyclophosphamide 60 mg/kg IV over 2 hrs (10 AM)
-1	Rest
0	Peripheral blood stem cell (and/or marrow) infusion

*Radiation therapy and the attending BMT physician may decide that patients may begin their TBI as an outpatient, and will then be admitted on day -4 to begin the Cy fluid flush.

1320 cGy will be administered in 8 fractions of 165 cGy each with 2 fractions being given each day.

4.3.2 Patients under the age of two, and patients who cannot receive TBI, will receive a cytoreductive regimen of "BU/CY" as per the Johns Hopkins University Hospital regimen.

Day	Agents
-7	*Busulfan 3.2 mg/kg in 4 divided doses (.8 mg/kg/dose IV q 6 hrs)
-6	Busulfan 3.2 mg/kg in 4 divided doses (.8 mg/kg/dose IV q 6 hrs)
-5	Busulfan 3.2 mg/kg in 4 divided doses (.8 mg/kg/dose IV q 6 hrs)
-4	Busulfan 3.2 mg/kg in 4 divided doses (.8 mg/kg/dose IV q 6 hrs)
-3	Cyclophosphamide 60 mg/kg/day IV over 2 hours
-2	Cyclophosphamide 60 mg/kg/day IV over 2 hours
-1	Rest
0	Stem cell infusion (>48 hours after the last dose of cyclophosphamide)

* Busulfan (intravenous BUSULFEX) dose, administration and phamacokinetic monitoring to be administered as described in MT2003-19S.

4.4 Infusion of Cryopreserved Autologous Stem Cells and/or Marrow

4.4.1 Stem cells are preserved using dimethyl sulfoxide (DMSO) as a cryoprotectant. DMSO may cause nausea during infusion. Patients should be premedicated with an anti-emetic one half hour prior to anticipated infusion. Autologous stem cells will be thawed on the transplant ward and infused intravenously.

4.4.2 The stem cells should be infused rapidly through a central venous catheter.

4.4.3 The entire line through which the stem cells are to be infused must be flushed with normal saline both pre and post-infusion. The remainder of the fluids administered to the patient may be of any composition deemed appropriate by the clinical physicians.

4.5 Supportive Care

4.5.1 Infectious Disease Prophylaxis:
Pneumocystis prophylaxis, CMV, fungal and bacterial prophylaxis will be performed according to current University of Minnesota guidelines.

4.5.2 Fluids
Adequate diuresis must be maintained before and after Cy administration to help prevent hemorrhagic cystitis. The recommended maintenance fluid is 3000-4000 $mL/M^2/24^o$. This rate should be started at least 10 hours before the first Cy dose and 24 hours after the last Cy dose. Cyclophosphamide has been associated with bladder cystitis and SIADH; therefore, serum electrolytes will be followed frequently, along with b.i.d. weights and strict intake and output. If patient develops any sign of fluid overload, appropriate measures will be taken to reduce fluid retention, such as use of diuretics. (See cytoxan fluid guidelines)

4.5.3 G-CSF Administration Post Transplant:
All patients will receive G-CSF (5 mcg/kg/day) subcutaneously or IV from day +1 until the ANC is $\geq$2,500 for 2 days.

4.5.4 All blood products administered after the initiation of primary chemotherapy will be irradiated (≥ 1500 rad). To prevent transfusion associated graft vs host disease.

4.5.5 Phenytoin:
Although patients receiving busulfan may on a rare occasion develop seizures, patients on this protocol will not receive anti-convulsants prophylactically as it is unknown whether anti-convulsants significantly change metabolism of busulfan in vivo. If seizures do develop, it is recommended that they be treated with phenytoin.

5.0 REQUIRED OBSERVATIONS

5.1 History: A complete medical history with full details of the patient's previous treatment and response including particularly:

5.1.1 Drugs (including previous chemotherapy regimens and total dose of anthracyclines).

5.1.2 Presenting WBC, FAB morphology and cytogenetics.

5.1.3 Cell surface markers on malignant cells.

5.1.4 Previous radiation (including dose and field size).

5.1.5 Previous CNS disease and treatment.

5.1.6 Previous other extramedullary relapses (e.g. chloromas).

5.1.7 Previous infections (specific organisms if known and antibiotic therapy).

5.1.8 Transfusions, including significant reactions.

5.1.9 Hemorrhage.

5.2 Physical examination of recipient; To include:

5.2.1 Height, weight, head circumference for patients < 4 years.

5.2.2 Tanner stage (breast, pubic) for patients <21 years.

5.3 Disease Status:

5.3.1

- If sufficient CD34+ cells are achieved in the PBSC harvest, the patient will proceed to transplant.

- If sufficient numbers of CD34+ are not achieved in the PBSC collection, and the marrow remains in remission, the patient will progress to bone marrow harvest. If disease progression is observed, either in the marrow or if extramedullary disease develops, the patient will be ineligible for transplant until further therapy is received and remission achieved.

5.4 Cytogenetic Studies:

5.4.1 Initial Testing:

All patients with previously documented cytogenetic abnormalities will have samples of blood (10 cc in sodium heparin tube) and 3-5 mL of heparinized marrow sent to the cytogenetics laboratory as part of their initial evaluation pre-BMT for metaphase and/or FISH analysis as indicated.

6.0 FOLLOW-UP STUDIES/RESPONSE EVALUATION

6.1 CBC, differential count, and platelets should be performed daily until ANC >500, then as needed until discharge. Thereafter, CBC's should be done every 1-2 months for the first two years after transplantation.

6.2 ALT, bilirubin, alkaline phosphatase, and electrolytes should be performed at least twice weekly during transplantation hospitalization.

6.3 Bone marrow aspiration and biopsy will be done as follows: day 28, at day 100, at 6 months at one year and 2 years from the date of transplantation, and then whenever clinically indicated. If a particular patient had a clonal cytogenetic abnormality pre-transplantation in the leukemia cells, then bone marrow cytogenetic studies should be obtained with each marrow aspirate.

6.4 Long-term follow-up studies to determine late effects of treatment:

6.4.1 Thyroid function studies (T4, TSH) will be performed yearly for two years.

6.5 Response Evaluation; Definition of outcomes :

6.5.1 Disease evaluation will be completed approximately 100 days after stem cell infusion and 6 months, 1 year, and until 2 years after infusion.

6.5.2 Time to treatment failure - from date of stem cell infusion to date of recurrence.

7.0 TOXICITIES AND COMPLICATIONS

7.1 Cyclophosphamide:

Bone marrow suppression, nausea, vomiting, diarrhea, mouth sores, alopecia, hemorrhagic cystitis, acute cardiac decompensation, and hyponatremia (usually responsive to limiting free water intake).

7.2 Busulfan:

Myelosuppression, mucositis, diarrhea, alopecia, pulmonary fibrosis, sterility, amenorrhea, and rarely seizures.

7.3. Etoposide (VP-16)

- Nausea, vomiting and diarrhea are common.
- Mucositis. Oropharyngeal mucosal inflammation may be severe with high-dose etoposide. This may require parenteral analgesia as the mucositis may be severe enough to prevent talking, swallowing or eating without pain.
- Secondary malignancy

7.4 Total Body Irradiation:

Nausea and vomiting, diarrhea, parotitis (rapid onset within 24-48 hours, usually self limiting), skin (generalized mild erythema), late effects (possible growth retardation, vertebral abnormalities, cataracts, probable increased risk of second malignant neoplasms, sterility).

7.5 G-CSF:

The administration of G-CSF can be associated with bone pain, headaches, body aches, fatigue, nausea, vomiting, insomnia, dyspnea and fever. Symptoms are usually minor and can usually be controlled with acetaminophen.

8.0 DRUG INFORMATION

8.1 Cyclophosphamide (Cytoxan (R), CPM) NSC - 6271. Commercially available.

8.1.1 Formulation

100.0 mg, 200.0 mg and 500.0 mg vials for IV use.

8.1.2 Storage

Room temperature.

8.1.3 Mixing

IV drug should be mixed with sterile water for IV use. Dissolves very slowly with cold water; it helps to warm water or warm vial after adding water.

8.1.4 Stability

IV solution should be used within 12 hours of mixing. May be stored at room temperature for 24 hours and 6 days when refrigerated.

8.1.5 Administration

By IV drip over 30-120 minutes.

8.1.6 Toxicity

Nausea and vomiting, alopecia, bone marrow depression, immunosuppression, hemorrhagic cystitis, SIADH, and rarely acute cardiac decompensation.

8.2 Busulfan (Myleran)

8.2.1 Formulation
IV solution.

8.2.2 Storage
Room temperature.

8.2.3 Stability
Note manufacturer's date.

8.2.4 Toxicity
Myelosuppression, mucositis, diarrhea, alopecia, pulmonary fibrosis, amenorrhea, azoospermia.

8.3 Etoposide (VP-16) Commercially available

8.3.1 Formulation
300 mg/m2 IV given on day 0 and day +1

8.3.2 Storage
Room Temperature

8.3.3 Administration
By IV infusion over 3 hours

8.3.4 Toxicity
Nausea, vomiting, diarrhea, myelosuppression, mucositis and secondary malignancy.

9.0 STUDY DESIGN

9.1 Objectives And Primary Outcome Variables:

1. Can sufficient PBMC be collected with the Cy/VP-16/G-CSF priming regimen? (from 1.1) The proportion of primed patients with adequate number of cells collected will be calculated.
2. What is rate of myeloid, platelet, and erythroid recovery (engraftment) (from 1.2). median days from BMT engraftment to cell recovery.
3. What is the rate of relapse? (from 1.3) will be delivered by Kaplan-Meier estimate.

9.2 Statistical Analysis:

This study defines a treatment plan for patients in whom transplantation is determined to be the preferred therapy. As a defined treatment plan, no statistical comparisons are planned.

9.3 Outcomes and Follow-up.

Patients will be followed for a minimum of 2 years post transplant and data will collected for a descriptive analysis of late effects of therapy. The percentage of individuals with various late effects will be examined, including thyroid function abnormalities, gonadal abnormalities, cataracts, pulmonary dysfunction, growth and development abnormalities, and second malignant neoplasms. Parameters will be observed for at least two years in individuals surviving post-transplantation.

After two years of follow up, patients will be monitored for survival data on through the BMT database.

10.0 DATA AND SAFETY MONITORING PLAN

This study will be in compliance with the Masonic Cancer Center's Data & Safety Monitoring Plan, which can be accessed at http://z.umn.edu/dmsp

For the purposes of data and safety monitoring, this study is classified as moderate risk. Therefore the following requirements will be fulfilled:

- The Masonic Cancer Center Data and Safety Monitoring Council (DSMC) will review the study's progress at least every 6 months with the understanding the Cancer Protocol Review Committee (CPRC) may require more frequent reporting.
- The PI will comply with at least twice yearly monitoring of the project by the Masonic Cancer Center monitoring services.
- The PI will oversee the submission of any event meeting the definition of reportable to the University of Minnesota IRB (http://www.research.umn.edu/irb/guidance/ae.html#.VC7xraI0-sh) with a copy to the MCC SAE Coordinator (mcc-saes@umn.edu) .

In addition, at the time of the continuing review with the University of Minnesota IRB, a copy of the report with any attachments will be submitted to the Cancer Protocol Review Committee (CPRC).

11.0 REFERENCES

1. Zittoun, R. A., Mandelli, F., Willemze, R., de Witte, T., Labar, B., et al. Autologous or allogeneic bone marrow transplantation compared with intensive chemotherapy in acute myelogenous leukemia. European Organization for Research and Treatment of Cancer (EORTC) and the Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto (GIMEMA) Leukemia Cooperative Groups [see comments], N. Engl. J. Med. *332:* 217-23, 1995.
2. Woods, W. G., Kobrinsky, N., Buckley, J. D., Lee, J. W., Sanders, J., et al. Timed-sequential induction therapy improves postremission outcome in acute myeloid leukemia: a report from the Children's Cancer Group, Blood. *87:* 4979-89, 1996.
3. Dinndorf, P. and Bunin, N. Bone marrow transplantation for children with acute myelogenous leukemia. [Review] [161 refs], Journal of Pediatric Hematology/Oncology. *17:* 211-24, 1995.

4. Christiansen, N. P. Allogeneic bone marrow transplantation for the treatment of adult acute leukemias. [Review] [145 refs], Hematology Oncology Clinics of North America. *7:* 177-200, 1993.
5. Mehta, J., Powles, R., Treleaven, J., Horton, C., Tait, D., et al. Long-term follow-up of patients undergoing allogeneic bone marrow transplantation for acute myeloid leukemia in first complete remission after cyclophosphamide-total body irradiation and cyclosporine, Bone Marrow Transplant. *18:* 741-6, 1996.
6. Gorin, N. C., Labopin, M., Fouillard, L., Meloni, G., Frassoni, F., et al. Retrospective evaluation of autologous bone marrow transplantation vs allogeneic bone marrow transplantation from an HLA identical related donor in acute myelocytic leukemia. A study of the European Cooperative Group for Blood and Marrow Transplantation (EBMT), Bone Marrow Transplant. *18:* 111-7, 1996.
7. Vowels, M. R., Lam-Po-Tang, R., Ford, D., Trickett, A., and Mameghan, H. Allogeneic and autologous bone marrow transplantation for acute non-lymphoblastic leukaemia, Journal of Paediatrics & Child Health. *30:* 319-23, 1994.
8. Dusenbery, K. E., Steinbuch, M., McGlave, P. B., Ramsay, N. K., Blazar, B. R., et al. Autologous bone marrow transplantation in acute myeloid leukemia: the University of Minnesota experience, International Journal of Radiation Oncology, Biology, Physics. *36:* 335-43, 1996.
9. Dusenbery, K. E., Daniels, K. A., McClure, J. S., McGlave, P. B., Ramsay, N. K., et al. Randomized comparison of cyclophosphamide-total body irradiation versus busulfan-cyclophosphamide conditioning in autologous bone marrow transplantation for acute myeloid leukemia [see comments], International Journal of Radiation Oncology, Biology, Physics. *31:* 119-28, 1995.
10. Ball, E. D. and Rybka, W. B. Autologous bone marrow transplantation for adult acute leukemia. [Review], Hematology Oncology Clinics of North America. *7:* 201-31, 1993.
11. Petersen, F. B., Lynch, M. H., Clift, R. A., Appelbaum, F. R., Sanders, J. E., et al. Autologous marrow transplantation for patients with acute myeloid leukemia in untreated first relapse or in second complete remission, Journal of Clinical Oncology. *11:* 1353-60, 1993.
12. Cahn, J. Y., Labopin, M., Mandelli, F., Goldstone, A. H., Eberhardt, K., et al. Autologous bone marrow transplantation for first remission acute myeloblastic leukemia in patients older than 50 years - a retrospective analysis of the european bone marrow transplant group, Blood. *85:* 575-579, 1995.
13. Brenner, M. K., Rill, D. R., Moen, R. C., Krance, R. A., Heslop, H. E., et al. Gene marking and autologous bone marrow transplantation. [Review], Ann N Y Acad Sci. *716:* 204-14, 1994.
14. Demirer, T., Buckner, C. D., Appelbaum, F. R., Petersen, F. B., Rowley, S., et al. Rapid engraftment after autologous transplantation utilizing marrow and recombinant granulocyte colony-stimulating factor-mobilized peripheral blood stem cells in patients with acute myelogenous leukemia, Bone Marrow Transplant. *15:* 915-22, 1995.
15. Henon, P. R. Peripheral blood stem cell transplantations: past, present and future. [Review] [119 refs], Stem Cells. *11:* 154-72, 1993.
16. Cassileth, P. A., Andersen, J., Lazarus, H. M., Colvin, O. M., Bennett, J. M., et al. Autologous bone marrow transplant in acute myeloid leukemia in first remission, Journal of Clinical Oncology. *11:* 314-9, 1993.
17. Woods, W. G., Kobrinsky, N., Buckley, J., Neudorf, S., Sanders, J., et al. Intensively timed induction therapy followed by autologous or allogeneic bone marrow transplantation for children with acute myeloid leukemia or myelodysplastic syndrome: a Childrens Cancer Group pilot study [see comments], Journal of Clinical Oncology. *11:* 1448-57, 1993.
18. Imrie, K., Dicke, K. A., and Keating, A. Autologous bone marrow transplantation for acute myeloid leukemia. [Review] [80 refs], Stem Cells. *14:* 69-78, 1996.

20. Bloomfield, C., Lawrence, D., Arthur, D., Berg, D., Schiffer, C., et al. Curative Impact of Intensification with High-Dose Cytarabine (HiDAC) in Acute Myeloid Leukemia (AML) Varies by Cytogenetic Group, Blood. *84:* suppl 1, 1994.
21. Mrozek, K., Heinonen, K., de la Chapelle, A., and Bloomfield, C. D. Clinical significance of cytogenetics in acute myeloid leukemia. [Review] [93 refs], Seminars in Oncology. *24:* 17-31, 1997.
22. Burnett, A. K., Goldstone, A. H., Stevens, R. M., Hann, I. M., Rees, J. K., et al. Randomised comparison of addition of autologous bone-marrow transplantation to intensive chemotherapy for acute myeloid leukaemia in first remission: results of MRC AML 10 trial. UK Medical Research Council Adult and Children's Leukaemia Working Parties, Lancet. *351:* 700-8, 1998.
23. To, L., Roberts, M., Haylock, D., Dyson, P., Branford, A., et al. Comparison of recovery times and supportive care requirements of autologous recovery phase peripheral blood stem cell transplants, autologous bone marrow transplants and allogeneic transplants, Bone Marrow Transplant. *9:* 277-284, 1992.
24. Demirer, T., Gooley, T., Buckner, C. D., Petersen, F. B., Lilleby, K., et al. Influence of total nucleated cell dose from marrow harvests on outcome in patients with acute myelogenous leukemia undergoing autologous transplantation, Bone Marrow Transplant. *15:* 907-13, 1995.
25. Roberts, M. M., Dyson, P. G., Willson, K., Juttner, C. A., and To, L. B. Peripheral blood stem cells mobilized from patients with acute myeloid leukaemia have different platelet repopulating abilities compared with those mobilized from patients with other diseases, Bone Marrow Transplant. *18:* 41-5, 1996.
26. Demirer, T., Buckner, C. D., Storer, B., Lilleby, K., Rowley, S., et al. Effect of different chemotherapy regimens on peripheral-blood stem-cell collections in patients with breast cancer receiving granulocyte colony-stimulating factor, Journal of Clinical Oncology. *15:* 684-90, 1997.
27. Demirer, T., Buckner, C. D., and Bensinger, W. I. Optimization of peripheral blood stem cell mobilization. [Review] [77 refs], Stem Cells. *14:* 106-16, 1996.
28. Meloni, G., Diverio, D., Vignetti, M., Avvisati, G., Capria, S., et al. Autologous Bone Marrow Tranplantation for Acute Promyelocytic Leukemia in Second Remission: Prognostic Relevance of Pretransplant Minimal Residual Disease Assessment by Reverse-Transcriptase Polymerase Chain Reaction of the PML/ARA□ Fusion Gene, Blood.*90:* 1321-1325, 1997.

APPENDIX I

Suggested Priorities for BMT: AML

Because of the differences in the treatment of subjects with these diseases based on age, active multicenter studies and U of Minnesota BMT Program scientific priorities, the following are suggested guidelines that should be considered in determining what type of BMT is considered.

AML

1. First remission: Autologous BMT for PBSC transplant for AML will be considered for adults with standard risk AML in CR1 with favorable cytogenetics t(8;21)

    - Second (or greater) remission: Subjects in ≥2nd CR are eligible for this autologous transplantation protocol, allogeneic transplantation is generally a proposed option.

Subjects with no donor available, or APL (M3) in molecular CR2 or those for whom allografting is unavailable or refused can be treated on this study.

APPENDIX II

Cell Collection, Storage and Use/Vascular Access for Apheresis

Peripheral blood stem cells will be collected using available apheresis machines. Currently apheresis will be performed using either antecubital veins or 13.5 Fr **Quinton/Davol** catheters if antecubital veins are not appropriate for apheresis collection. A minimum of $\geq 2.5 \times 10^6$ CD34+ cells/kg in the 3-6 apheresis collections will be required to proceed. If $\leq 2.5 \times 10^6$ CD34+ cells/kg are collected, the patient will proceed to bone marrow harvest to obtain additional nucleated cells. All collected cryopreserved cells are to be infused on day 0.

APPENDIX III
Required Studies (within 30 days of scheduled date)

	Pre	D 21	D 28		D 100	6 mo	1 yr		2 yr
Bone Marrow:									
Trephine	X		X			X	X		X
Aspirate	X		X			X	X		X
Chromosomes			X			X	X		X
Spinal Tap :	X								
Prot., gluc., cell ct, cytospin									
MUGA	X								
PFT	X								
EKG	X								
Chest x-ray	X				X				
UA	X				X		X		
Blood Work :									
CBC, Plt, Diff	X	X	X		X	X	X		X
BUN/Creat, GNE	X				X		X		
ALT, Bili, Alk Phos	X				X		X		
HBSAG, HBCAB, Hep. C	X								
Anti HTLVI, HIV I/II	X								
HIV Antigen	X								
RPR	X								
CMV, HSV Antibody	X								
PT, PTT, TT, INR	X								
Uric Acid	X								
T_4, TSH							X		X
ABO, Rh	X								

APPENDIX IV: TBI GUIDELINES

Fractionated Total Body Irradiation (In Lateral Position)

1320 cGy administered in an 8 fractions of 165 cGy each with 2 fractions being given each day. The interval between fractions should be at least 4 hours.

Total body irradiation is given at a dose rate of 10-19 cGy/minute prescribed to the midplane of the patient at the level of the umbilicus.

The total body irradiation will be delivered with right and left lateral fields, with the patient supine on a specially designed couch.

Based on measurements of transverse thickness, aluminum compensators will be used as necessary to deliver a uniform dose within ±10% of the prescribed dose . Usually head/neck, leg and lung compensators are used (although based on calculated mid-mediastinal doses, lung compensators are often not needed).

TBI will be given by 6, 10, or 18 MV x-ray beams. The energy used will be based on the calculated dose to the midline at points up and down the patient's torso. The lowest energy that gives 90-100% of the prescription point dose will be used.

A beam spoiler will be used for skin sparing.

Half value layer lung and kidney blocks will not be utilized.