CITY OF HOPE NATIONAL MEDICAL CENTER
1500 E. DUARTE ROAD
DUARTE, CA 91010

DIVISION OF HEMATOLOGY AND HEMATOPOIETIC CELL TRANSPLANTATION

TITLE: Autologous Stem Cell Transplantation for Non-M3 Acute Myeloid Leukemia (AML) in First Remission in Patients ≤ 60 Years of Age Using Busulfan/Fractionated Total Body Irradiation (FTBI) and VP16 as the Preparative Regimen

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Amendment 01	8/7/00	Version: 01
Amendment 02	1/30/01	Version 02
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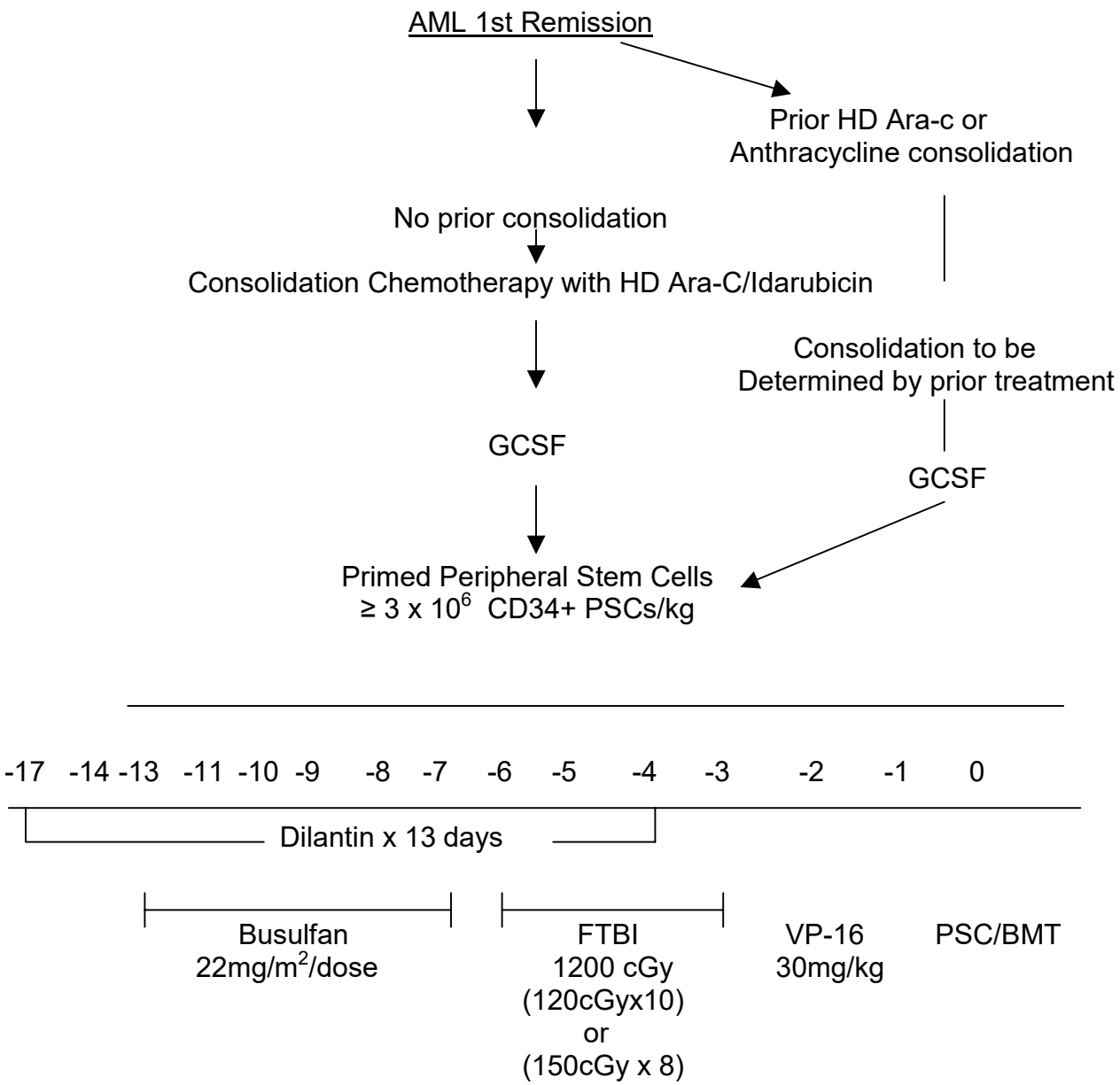
SITE: Hematological
STAGE: Acute Myeloid Leukemia
MODALITY: Autologous BMT
TYPE: Phase 2

PRINCIPAL INVESTIGATOR:	Anthony Stein, M.D.
COLLABORATING INVESTIGATOR(S):	Stephen J. Forman, M.D.
	Joyce Niland, Ph.D.
PARTICIPATING CLINICIANS:	Ravi Bhatia, M.D.
	Amrita Krishnan, M.D.
	Auayporn Nademanee, M.D.
	Ryotaro Nakamura, M.D.
	Leslie Popplewell, M.D.
Department of Medical Oncology	George Somlo, M.D.
	Tim Synold, Ph.D.
Department of Radiation Oncology	Nayana Vora, M.D.
	Firoozeh Sahebi, M.D.
	Ricardo Spielberger, M.D.
Division of Pediatrics	Joseph Rosenthal, M.D.
City of Hope Samaritan Bone Marrow	Joseph C. Alvarnas, M.D.

SCHEMA



Rev. 11/7/01

IL-2

Induction:

IL-2, 9mIU/m^2/d c.i.v.i. x 96 hours (days 1-4)
Days 5-8 Rest

Maintenance

IL-2, 1.6 mIU/m^2/d c.i.v.i. x 240 hours (days 9-18)

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1.0 OBJECTIVES

a. To evaluate the efficacy and toxicity of fractionated total body irradiation (FTBI) in combination with busulfan (BU) dosage targeted to AUC 700-900 and VP-16 followed by post-BMT interleukin-2 (IL-2) as a preparative regimen for autologous BMT for patients with AML in 1st CR.

b. To estimate the long term disease free survival for patients ≤ 60 years of age with AML in first remission receiving an autologous BMT utilizing primed peripheral stem cells following consolidation therapy with high dose ara-c and Idarubicin or high dose Ara-c alone.

c. To further evaluate the effect of prognostic factors e.g. cytogenetics, WBC at presentation, number of courses of induction therapy to enter remission on the outcome of autologous BMT and AUC of Busulfan.

2.0 BACKGROUND

Currently between 60-80% of adults with AML who are under 60 years of age achieved complete remission (CR) with intensive chemotherapy. However, only a fraction of these patients enjoy long term disease-free survival and are cured of the disease. A number of studies involving large groups of patients have demonstrated that approximately 20% of patients who had attained CR will remain free of disease following treatment with "standard" post remission chemotherapy. [1-4] More recent studies suggest that if post remission chemotherapy is intensified, as many as 30% of remission patients may remain free of disease. It has been suggested that the use of high dose ara-c in post remission chemotherapy may increase long-term disease free survival to as much as 40%.[5,6] The major obstacle for long term survival in patients treated with chemotherapy is leukemic relapse which affects between 60-75% of patients.

The results of allogeneic bone marrow transplantation for AML in remission demonstrates that the risk of leukemic relapse can be substantially reduced when bone marrow rescue allows escalation of the dose of chemoradiotherapy. Adults receiving allogeneic transplant for AML in first complete remission have long term disease free survival rates of approximately 45-70% in a large number of studies.[3,7-11] Most studies show a leukemic relapse rate of approximately 10-20%. However, allogeneic bone marrow transplantation has limitations, and because of high morbidity of therapy, allogeneic transplantation is restricted to adults under the age of 50. Furthermore, only approximately 1/3 of potentially eligible patients in this age group have histocompatible donors. Thus, less than ¼ of adults under the age of 50 will be candidates for allogeneic transplantation. Furthermore, the success of allogeneic transplantation has been hindered by an early mortality rate due to treatment related complications, particularly graft versus host disease (GVHD) and interstitial pneumonia. Approximately 15-30% of adults die within the first 3 months of transplantation because of such complications. Progress in the prevention and treatment of GVHD may reduce this high early mortality rate.

Autologous bone marrow transplantation is attractive because two of the major problems with allogeneic transplantation are avoided. There is no need to find a

matched donor, and the absence of immunosuppressive therapy and GVHD decreases the morbidity and mortality rate. However, there are several theoretical problems in autologous transplantation as therapy for acute leukemia. One potential problem is the absence of graft versus leukemia (GVL) effect. Analysis of results in Seattle for patients without GVHD compared with GVHD showed relapse rates of 65% versus 35% suggesting that GVHD is accompanied by beneficial GVL effect.[12] Further support for the GVL concept comes from the analysis of relatively a small group of patients treated in remission with marrow transplantation utilizing identical twin donor (who cannot have GVHD) who have a 50% relapse rate.[13] Thus, without an improved anti-leukemic effectiveness of the preparative regimen one would expect a leukemic relapse rate of approximately 50% from auto transplants drawing on the analogy to syngeneic transplantation. Furthermore, one must deal with the risk of infusing viable clonogenic leukemic cells even if marrow morphologically demonstrating remission. Not only may a small contaminating leukemic cell population be missed but a report suggests that even morphological normal cells may be derived from a malignant clone.[14] If leukemic cells were infused during auto transplant the relapse rate would be expected to be even higher than 50%.

Studies utilizing autologous BMT for AML in first remission have reported disease free survivals of 34-80% (with varying follow-up intervals).[15-20] Although each trial demonstrates the potential efficacy of this approach chosen, many of the studies have been criticized because of selection bias. Results of the MRC AML 10 trial show that the addition of autologous BMT to intensive chemotherapy substantially reduced the risk of relapse when compared to chemotherapy alone.[21]

Relapse is the major cause of failure of ABMT. The lowest relapse rates in AML occur in allogeneic BMT compared to syngeneic BMT, demonstrating the role of graft versus leukemia effect in preventing relapse. Since relapses after autologous hematopoeitic cell transplant tend to occur early, and since IL-2 responsive lymphocytes have been detected in circulation within 2-3 weeks after transplantation of autologous marrow or peripheral blood stem cells, IL-2 has been administered early, after the patients have recovered from transplant related toxicities, at a time when tumor burden is still minimal but before relapses are likely to occur. Several phase I studies have identified a maximum tolerated dose of IL-2 which can be administered after autologous stem cell transplant and documented its immunomodulatory effects. Patients usually exhibit transient early lymphopenia followed by a rebound lymphocytosis after stopping IL-2. This rise reflects increases in the number of cells expressing CD8 + T cells and CD16 + and CD56 + activated natural killer cells, with concomitant enhanced ability to lyse tumor.[22-25]

3.0 Institutional Experience and Rationale for Proposal

From January 1987 through July of 1998, nine patients underwent autologous bone marrow transplant for AML in first remission using the conditioning regimen consisting of busulfan and VP-16. Four of these nine patients are in remission now for more than 10 years, one patient died a toxic death during the neutropenic phase, there were no other unexpected toxicities.

Between March of 1989 and November 1993, the conditioning regimen was changed to FTBI 1200cGy/VP-16 60mg/kg and Cyclophosphamide 75mg/kg. We intended to transplant 60 adult patients with AML in first remission. All 60 patients underwent consolidation chemotherapy with high dose Ara-C (HD Ara-C) 3 gm/m^2 8-12 doses. Following this consolidation treatment, bone marrow was harvested and cryopreserved. Ten patients relapsed prior to being transplanted. 44 patients underwent ABMT with a median follow-up time of 37 months. The cumulative probability of disease free survival at 24 months in the intent to treat group, is 49 percent and in those actually undergoing ABMT was 61%. The probability of relapse was 44% and 33% for the intent to treat and autologous BMT patients, respectively.

In an effort to try and improve on these results Idarubicin was added to high dose ara-c as part of the consolidation regimen and interleukin-2 was added to post BMT therapy to try and decrease the relapse rate. From August 1994 to the present time 58 patients have been evaluated with the intent to proceeding to an autologous stem cell transplant. For the intent to treat group the cumulative probability of disease free survival at three years is 67% and relapse rate 31%. For the 50 patients actually undergoing autologous stem cell transplant the cumulative probability of disease free survival at three years is 72% and their relapse probability is 27%.

Rev 5/15/01

Patients with good risk cytogenetics t (8;21) or INV 16 or t (16;16) have been shown to have improved DFS when treated with repeated cycles of high dose Ara-C alone.[31,32] At City of Hope fifty six patients were treated with high dose Ara-C/idarubicin consolidation treatment with hematological recovery as follows:

ANC >500/µl median of 26 days [range 17,62]
ANC >1000/µl median of 27 days [range 18,65]
Untransfused platelets >20,000/µl median of 37 days [range 19,62]

Due to the long hematological recovery and no literature evidence for adding idarubicin to the consolidation treatment, the protocol will be amended to omit idarubicin for patients with good risk cytogenetics.

At City of Hope between 8/92 and 10/98 61 patients were entered on a phase I study of escalating doses of busulfan in combination with TBI and VP-16 in patients with advanced hematological malignancies in an effort to try and improve the outcome of allogeneic bone marrow transplant in these poor risk patients. The MTD was defined at 11 mg/kg of busulfan in combination with FTBI 1200 cGy and VP-16 60mg/kg. The median AUC was 892µM*min (460-1267) for this group of patients. 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 an improved disease free survival + relapse was Busulfan dose of 7-8mg/kg. An AUC of 700-950µM*min demonstrated a trend to a decreased relapse rate and improved DFS.

Allogeneic and autologous BMT studies performed in approximately 100 patients the I/V formulation has been shown to have more predictable pharmacokinetic properties than the oral preparation resulting in a better toxicity profile.[26-28]

Relapse is still the major reason for failure for BMT. In an attempt to try and decrease the relapse rate post autologous stem cell transplant we plan to substitute intravenous busulfan for cyclophosphamide in the conditioning regimen.

4.0 Drug Information

4.1 Cytosine Arabinoside (cytarabine, Ara-C, cytosar) NSC #63878

4.11 Source of Pharmacology: Deoxycytidine analogue which is metabolized to Ara CTP, a substance which inhibits DNA polymerase. It is S-phase-specific, and thus affects DNA synthesis. It has an initial half-life of about 15 minutes, with a secondary phase of about two hours. Rapidly catabolized by hepatic cytidine deaminases to Ara-U. Intrathecally administered doses are catabolized and eliminated more slowly with a half-life of 1-11 hours.

4.12 Formulation and Stability: A freeze-dried powder available in 100 mg and 500 mg vials with diluent which contains 0.9% benzyl alcohol in water. The unreconstituted form of the drug is stable at room temperature for at least two years. Reconstitute with 5 ml of diluent to 100 mg vial and 10 ml to the 500 mg vial. Also available in 1g and 2g vials without diluent. Reconstitute with 10 ml and 20 ml sterile water or bacteriostatic water. The reconstituted solution is stable at room temperature for 48 hours. Solutions that develop a slight haze should be discarded. Infusion solutions containing up to 500 µg (0.5 mg) of cytarabine per ml are stable at room temperature for seven days.

Revised 3/11/02

4.13 Supplier: Commercially available and approved by the FDA for the purposes indicated.

4.14 Toxicity: Acute DLT - severe leukopenia and thrombocytopenia. Nausea and vomiting may be dose-limiting at higher doses. Other adverse reactions include immunosuppression, anorexia, stomatitis, mild oral ulcerations, flu-like syndrome with fever, and alopecia. Diarrhea, fever, somnolence, conjunctivitis, ataxia, encephalopathy, or veno-occlusive disease can also develop. Chronic administration may cause mild gonadal dysfunction. IT Administration: Fever, headache, vomiting, and pleocytosis. On rare occasions meningismus, convulsions, paresis, and cardiac arrest have been reported.

4.15 Route of Administration: IV infusion, IT. When given in high doses, antiemetics and dexamethasone eye drops are indicated. Intrathecal Administration: IT cytarabine should be reconstituted in physiologically buffered diluents (lactated Ringer's) or patient's own CSF. The diluent provided should not be used for IT administration.

4.2 Idarubicin (4-demethoxydaunorubicin, Idamycin) NSC #256439

4.21 Source of Pharmacology: Idarubicin is an analogue of the anthracycline daunorubicin. It binds to DNA in a similar manner to daunorubicin and also inhibits nucleic acid polymerase. It has similar activity to daunorubicin in inhibiting DNA synthesis, but is more active in inhibiting RNA synthesis.

Idarubicin is more lipophilic than daunorubicin and has an extensive tissue distribution of approximately 1000 L/M^2. It is metabolized to idarubicinol, which also has antileukemic activity. The clearance and consequently the half-life show marked inter-individual variability and average 679 ml/min/M^2 and 17.6 hours for that parent drug with a terminal half-life of 56.8 hours for idarubicinol. The excretion is via hepatic (biliary) route. Renal excretion of Idarubicin is minor, therefore renal dysfunction would be expected to have little effect on its disposition. The magnitude of hepatic function and/or blood flow could potentially influence the disposition of Idarubicin.

4.22 Formulation and Stability: Idarubicin is supplied in vials of 5 and 10 mg as a sterile lyophilized powder for injection. Its shelf-life at room temperature is 36 months for the 5 mg vial and 24 months for the 10 mg vial.

Solution Preparation: Idarubicin 5 mg and 10 mg vials should be reconstituted with 5 ml and 10 ml respectively of 0.9% sodium chloride for injection or sterile water for injection to give a final concentration of 1 mg/ml. Bacteriostatic diluents are not recommended.

Revised 3/11/02

4.23 Supplier: Commercially available and approved by the FDA for the purposes indicated.

Stability: Constitution of the vials as recommended results in a solution which is chemically stable for 72 hours at room temperature. Further dilution of the constituted solution (0.01 mg/ml) results in a solution which is mildly light sensitive and should be protected from light if being administered more than six hours after its preparation.

4.24 Compatibility/Incompatibility: 0.9% Sodium chloride injection = compatible; 5% dextrose = compatible; Ringer's lactate = unknown; dextrose/saline mixture = compatible; heparin - incompatible.

4.25 Toxicity: Acute toxicity includes myelosuppression, especially leukopenia and thrombocytopenia. Non-hematologic toxicities include nausea, vomiting, alopecia, diarrhea, fatigue, stomatitis, fever, and anorexia. These non-hematologic toxicities are rarely severe. Transaminase elevation has also been seen. Renal toxicity is rare. Idarubicin shares the cardiac toxicity of other anthracyclines, and has caused clinical congestive heart failure, most commonly in patients who have received other anthracyclines.

4.26 Route of Administration/Precautions: **IV or PO. Idarubicin should be administered by IV slowly (over 5-15 minutes) into the tubing of a freely-running IV infusion of compatible fluids.

**Avoid extravasation. If extravasation occurs: It is recommended that intermittent ice packs (1/2 hour immediately, then 1/2 hour 4x/day for 3 days) be placed over the area of extravasation and that the affected extremity be elevated.

**Monitoring of cardiac function is recommended before each additional course of treatment in patients who have received a total of 120 mg/M^2 of Idarubicin.

4.3 Busulfan

4.31 Busulfan is a bifunctional alkylating agent. In aqueous media, busulfan hyrolyses to produce reactive carbonum ions that can alkylate DNA.

4.32 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 4ºC for at least twelve months. Ampules should be stored refrigerated at 2-8ºC. 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.

4.33 Administration: Each dose of the drug will be given by slow central intravenous infusion over 2 hours. <u>Caution: Do not administer as an intravenous push or bolus</u>.

Revised 3/11/02

4.34 Supplier: This drug is commercially available manufactured by Orphan Medical Inc. It is not approved by the FDA for the purposes indicated.

4.35 Toxicity: Toxicity from busulfan includes:

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 HC1.
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.

4.4 Interleukin-2 (IL-2) NSC #373364 (Chiron Corporation, Cetus Oncology Unit, Emeryville,California)

4.41 Drug Formulation and Procurement: The recombinant mutein IL-2 to be used in this trial is commercially available. It was produced in E. coli transfected with the gene for IL-2 isolated from the Jurkat cell line. The IL-2 has been purified to homogeneity and its biological characteristics and *in vivo* effects in animal models have been well studied.

Less than 0.04 mg of endotoxin are present per $1x10^6$ units of lyophilized IL-2 in the vial along with 5% mannitol and approximately 50µg of SDS. The biological activity of IL-2 is to defined as 18 million International Units (IU)/mg protein.

4.42 Drug Toxicity: IL-2 toxicities may include: fever, chills, nausea, vomiting, fatigue, headache, myalgia, arthralgia, weight gain hepatic toxicity, rash, depression of myocardial function, arrhythmias, thrombocytopenia, anemia, hypotension, renal toxicity, diarrhea and transient confusion or psychosis.

4.43 Drug Storage, Reconstitution and Stability

4.43.1 Stability Studies: Potency data indicates that lyophilized, recombinant IL-2 is stable at 2-8° C for two years. After reconstitution in 1.2 ml of sterile water for injection, it is stable for at least 24 hours at room temperature.

4.43.2 Reconstitution: Recombinant IL-2 is supplied as a lyophilized cake in vials. Reconstitute each vial as follows:

Remove flip-top plastic cap and swab the target area of the stopper with antiseptic.

Antiseptically inject an appropriate volume of sterile water for injection into vial to dissolve the lyophilized cake. Since contents of vial are under vacuum, the diluent should be directed against the side of vial to avoid excess foaming.

Mass units indicated on the vial label represent the amount of IL-2 that can be recovered from the vial when reconstituted, as shown below.

Vial Label	Volume	Mass units/ml
1mg	1.2ml	1.0mg/ml

4.43.3 Dilution Procedure: Recombinant IL-2 can be diluted in D5W for intravenous infusion. Dilutions in other solutions or mixture with other drugs should be avoided. Each day's dose will be prepared in a 50-ml cassette for delivery at a continuous infusion rate of 2ml/hour, using the Pharmacia Deltec CADD infusion pump.

Revised 3/11/02

4.43.4 It is not approved by the FDA for the purposes indicated.

4.5 VP-16 (epipodophyllotoxin, etoposide, 4'-demethyl-9 (4,6-o-β) d-ethylideneglycopyranoside). VP-16 is not approved by the FDA for the purposes indicated. It has been commonly used in leukemia transplant conditioning regimens for at least 10 years.

Revised 3/11/02

4.51 Drug Formulation and Procurement: VP-16 is supplied by Bristol Laboratories in a 100 mg ampule in 5 cc of a solution containing citric acid, 10 mg; benzyl alcohol, 150 mg; polysorbate 80, purified, 250 mg; polyethylene glycol 300, 3.75 gm; absolute alcohol q s., 5 cc.

4.52 Drug Toxicity: Myelosuppression, primarily granulocytopenia, is the dose-limiting toxicity. Gastrointestinal toxicity at high doses includes nausea, emesis and mucositis. Reversible hepatotoxicity may occur at very high doses. The acute side effects of occasional bronchospasm and hypotension are avoided by slow intravenous administration.

4.53 Drug Storage, Reconstitution and Stability: The contents of the ampule are diluted with 50 volumes of NaCl solution for injection, USP, and administered by slow intravenous infusion. Patients will receive the drug through a central venous catheter at a rate of 30 mg/kg/4 hours.

Revised 3/11/02

5.0 PATIENT ELIGIBILITY

Rev. 11/7/01 Each of the criteria in the following section must be met in order for a patient to be considered eligible for consolidation therapy and autologous stem cell transplantation.

Revised 8/7/00 a). Patients age $\geq$ or equal to 16 and patients should have not reached their 61st birthday (physiological age 60).

b). Patients in first remission who are treated for acute myelogenous leukemia AML, FAB types, M0-M7. M3 will be excluded.

Revised 11/19/02 c). A marrow aspiration and biopsy demonstrating a complete hematological remission. Patients need to have a normal platelet count within five days of starting consolidation chemotherapy.

d). No cytogenetic abnormalities in the remission marrow.

Revised 3/11/02

e). Patients who are in first complete remission of acute myelogenous leukemia who have received consolidation therapy prior to coming to transplant center will be eligible for the protocol but will evaluated separately.

f). Patients must be in complete remission for less than 6 months. Patients in remission for longer than 6 months may be placed on the study after review by P.I. and will be evaluated separately.

Exclusion Criteria:

1. Prior myeloproliferative disorder such as CML, myelofibrosis, essential thrombocytosis, or polycythemia vera.

2. Prior myelodysplasia or secondary leukemia.

3. Any severe chronic medical or psychological illness as in the judgment of the physician would jeopardize the ability of the patient to tolerate aggressive chemotherapy. Patients must have FEV_1, >60% + DLCO >50% a cardiac ejection fraction $\geq$ 50% and creatinine clearance of >60ml/min.

Revised 3/11/02

4. HIV positive

5. Pregnancy

Revised 8/7/00

6.0 PLAN OF TREATMENT

Revised 8/7/00

Revised 3/11/02

6.1 Pre-Consolidation Evaluation: Will be performed 4 weeks prior to treatment except for the following: 1). Bone marrow aspirate and biopsy + cytogenetics within 14 days of starting treatment. 2). 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 should be given to prior chemotherapy, height, weight, and body surface area should also be noted.

b). Patients will have the following lab tests performed; CBC, differential, platelet count, comprehensive metabolic panel, pregnancy test, 24 urine for creatinine clearance, hepatitis panel, HIV antibody.

Revised 8/7/00
Rev. 11/7/01

c). Lumbar puncture will be performed in patients with FAB M4, M4eo + M5, patients with WBC at diagnosis > 50,000 and patients with cutaneous involvement. 12 mg of intrathecal methotrexate should be given at the time of the lumbar puncture. This can be done as an inpatient at time of consolidation treatment.

Rev. 11/7/01

d). Pulmonary function tests.

e). Echocardiogram or MUGA scan.

f). Bone marrow studies 1). aspirate and biopsies for morphology and 2). Cytogenetic analysis.

g). CT scan of chest, abdomen and pelvis.

Rev. 11/7/01

The following pre-study tests should be obtained within 28 days of starting treatment in accordance with good medical practice. Results of these tests do not determine eligibility and minor deviations would be acceptable if they do not impact on patient safety in the clinical judgement of the treating physician. The Study Coordinator must be contacted if there are significant deviations in the values of these tests.

Uric acid, LDH, phosphorous, cholesterol, magnesium, urine analysis, herpes simplex titer, CMV titer, immunoglobulin levels, thyroid panel (free T4 and TSH), chest x-ray and EKG, HLA typing of patient and siblings.

6.2 Consolidation Chemotherapy

6.21 Patients who have received consolidation treatment prior to coming to City of Hope will be evaluated to determine how many doses of HD Ara-c and anthracycline they have received. Patients who have received more than 200mg/m^2 of anthracycline will not receive idarubicin. Patients who have received 8 or more doses of HD Ara-c will have GCSF primed cells collected. Patients who have had < 8 doses of HD Ara-C will receive additional HD Ara-C not to exceed 12 doses [36grams/m^2].

Rev. 05/06/03

6.22 Patients who have received no consolidation treatment will follow the following treatment plan:

Revised 8/7/00

a). Beginning 4 hours prior to starting Ara-C all patients will be adequately hydrated. All patients will require anti-emetics to control nausea and vomiting. Patients will undergo a neurological assessment prior to each dose of Ara-C for evaluation of cerebellar symptoms.

Revised 8/7/00

b) Patients will receive Ara-C 3 gm/m^2 IV over 3 hours every 12 hours for a total of 8 doses. (Day 1-4). Patients age 55 to 60 will receive 2gm/m^2 of Ara-C.

Revised 5/4/01

c) Idarubicin 12 mg/m^2 will be given by slow intravenous infusion (5-10 minutes) after Ara-C dose 1, 3, 5. (Day 1-3). Patients with good risk cytogenetics (t 8;21) or inv 16 or (t 16;16) will not receive the idarubicin.

Revised 3/11/02

d) GCSF 10 µg/kg IV or subcutaneously in 2 divided doses will be started 7 days after Ara-C completed and continued until peripheral stem cell collections are completed.

e) Once patients' WBC >5000/µl peripheral stem cells will be collected with the goal collecting 3 x 10^6/kg CD34 cells (target 3-5 x 10^6/kg). If stem cell collections are poor the stem cell collection should then be delayed until the platelet count recovers to > 50,000. The G-CSF

dose can be increased to 16 mcg/kg/day subcutaneously in 2 divided doses [or I/V depending on transplant center standard protocol.

Revised 8/7/00

Revised 1/30/01

f) CBC, platelet count daily, (differentials per MD discretion), comprehensive metabolic panel plus uric acid, LDH, phosphorous and cholesterol, Mg^{++} are drawn daily during chemotherapy then every Monday, Wednesday, Friday during consolidation therapy.

6.3 Dose Adjustments

a) Idarubicin		
	Total Bilirubin	Dose Reduction
	≤ 2.5	0
	$> 2.5 \leq 5$	50%
	>5	100%
b) Ara-C		
	Creatinine	Dose Reduction
	< 1.3	0
	1.3 – 1.4	33%
	1.5 – 2.0	66%
	> 2.0	Hold Dose

For any dose adjustment reduction an attempt will be made to give a total Ara-C dose of 24 gm/m^2, i.e. give difference on day 5 and 6. No dose should exceed 3gm/m^2.

6.31 Supportive Care:

a) Decadron eye drops are given throughout the treatment with Ara-C and should be continued for four days following the completion of Ara-C.

b) All patients will have a right atrial catheter inserted prior to beginning or during the consolidation chemotherapy.

Revised 8/7/00

c) All patients will receive systemic fungal prophylaxis with Amphotericin B (0.15 mg/kg/d), liposomal Amphotericin B or Itraconazole 200 mg b.i.d. following completion of chemotherapy until normalization of ANC's.

d) All patients will receive filtered and irradiated (2500 cGy) blood products. Platelet and red cell transfusions will be given as clinically indicated.

e) All patients should receive hyper alimentation until oral caloric intake is adequate to meet the patients nutritional needs.

6.4 Cryopreservation of Peripheral Blood Stem Cells

At least 3 x 10^6 CD34 positive cells/kg will be collected with a target range of 3 to 5 x 10^6 $CD34^+$ cells/kg. Enriched mononuclear cells/CD34 preparation is

obtained by peripheral blood apheresis. Cells are cryopreserved according to participating site institutional standard operating procedure after review and approval of the P.I. (Anthony Stein, M.D.) and the City of Hope Stem Cell lab director (Andrew Walton, telephone: (626) 359-8111 Ext. 62695, fax number: (626) 930-5472).

6.5 High Dose Therapy Treatment

Revised 8/7/00

6.51 Pre-Transplant Evaluation: Within 4 weeks of starting busulfan.

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.

Rev. 11/7/01

Revised 8/7/00

b) CBC with differential, platelet count, comprehensive metabolic panel.

Revised 3/11/02

c) Chest x-ray

d) MUGA scan or 2D-Echocardiogram.

Revised 8/7/00

e). Bone marrow aspirate and biopsy, and cytogenetics needs to be done within four weeks of starting busulfan.

Rev. 11/7/01

The following pre-study tests should be obtained within 4 weeks of starting treatment in accordance with good medical practice. Results of these tests do not determine eligibility and minor deviations are acceptable if they do not impact on patient safety in the clinical judgement of the treating physician. The Study Coordinator must be contacted if there are significant deviations in the values of these tests.

f). Uric acid, LDH, phosphorous, cholesterol, magnesium, urine analysis, herpes simplex titer, CMV titer, immunoglobulin levels, thyroid panel (free T4 and TSH), chest x-ray and EKG, HLA typing of patient and siblings.

g). PFT's as indicated.

Patients who are evaluated at transplant center after already receiving consolidation therapy are required to have the same tests performed pre consolidation treatment. (6.1 a-g)

*If patients tests are performed and the transplant is delayed due to non medical causes [e.g. insurance] and patient receives no further treatment then echocardiogram, PFT's, chest x-ray and antibody titres do not need to be repeated within 3 months.

6.52 Preparative Chemotherapy Regimen:

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Friday/Day –17

Begin Dilantin 300mg p.o. t.i.d. x 1 day , then 300mg p.o./I/V daily x 13 days.

Tuesday/Day –13

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 over 2 hours as a single dose. The I/V dose is calculated as follows:

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

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

2. Dose of IV busulfan that is equivalent to a total dose of 11mg/kg of the oral dose is: 22 mg/m^2 per dose. Blood levels will be obtained with the first dose as per appendix 1. Busulfan levels will be performed at COH (Dr. David Senitzer, City of Hope National Medical Center, 1500 E. Duarte Road, Duarte, California 91010 and will only be sent to Quest Diagnostics as a back-up. Call Gary (626) 256-8621 24hrs before shipping samples.

Wednesday/Day –12

Busulfan AUC will be calculated by standard methods available in the City of Hope Analytical Pharmacology Core Facility (APCF). The resulting AUC will be used to determine the dose required to achieve an AUC of 800 μM* min according to the following formula:

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

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

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Thursday/Day –11

If the adjusted dose of busulfan is indicated, the adjusted dose will be given and blood levels will be repeated. Further dose adjustments will be performed if AUC>1000.

Friday/Day –10	Patient admitted to BMT or outpatient department to receive further doses of Busulfan. Resume busulfan once PK results are known.
Revised 8/7/00	Busulfan dose is resumed and is repeated every 6 hours for a total of 16 doses (including test dose(s). Last dose is given at midnight on day –7.
Tuesday/Day-6	Fractionated TBI will be given at 120 cGy per fraction for a total of 4 days [day –6, -5, -4, -3] for a total of 10 fractions for a total dose of 1200cGy. Or FTBI will be given at 150cGy per fraction x 8 fractions for a total of 4 days (-6,-5, -4,-3) total dose 1200 cGy Appendix IIa.
Saturday/Day –2	VP-16 30mg/kg based on adjusted ideal body weight will be administered.

CALCULATIONS OF IDEAL BODY WEIGHT

1. Male IBW = 50kg + 2.3 kg(height [in] - 60)
2. Female IBW = 45.5 kg + 2.3kg (height [in] - 60)

Sunday/Day –1	Rest
Monday/Day 0	The frozen peripheral blood cells will be transported to the transplant unit and thawed in a water bath outside the patient's room. Each bag will be infused undiluted rapidly through standard IV tubing without a filter. *Premeds for stem cell infusion will be given as per the standard operating procedure of the respective transplant center. A recommended regimen is hydrocortisone and 25mg of diphenhydramine and Mannitol 12.5gm per MD discretion. Those patients who have $\geq$ $3x10^6$ CD34 cells/kg PSC's will receive PSC's only. All other patients will receive both primed PSC's and bone marrow.
Revised 3/11/02	
Saturday/Day +5	Start GCSF 5µg/kg IV or subcutaneously.

6.53 Central Nervous System Therapy

In general, no specific CNS therapy will be administered. Patients with CNS disease at initial diagnosis will receive five weekly doses of intrathecal methotrexate (12 mg) both before and after autologous bone marrow transplantation. These patients will then receive monthly doses of intrathecal methotrexate (12 mg) during the first year of remission.

6.54 Supportive Care During Transplant:

On day –6 menstruating females will start provera 10 mg p.o. daily and Nystatin vaginal suppositories 1 b.i.d.. Prophylactic antibiotics: Levofloxacin 500 mg p.o or IV qd until ANC >500, Bactrim DS 1 tablet p.o. b.i.d. will be started at start of conditioning regimen and continued until day - 2.

Prophylaxis for herpes simplex: Patients with positive ab titres for herpes simplex will receive acyclovir 250mg/m^2 starting day –1 + continue until Day +20 or resolution of mucositis.

Hyperalimentation will be given while patient is unable to eat.

Prophylaxis for veno occlusive disease: Heparin 100 units/kg/day continuous infusion from start of conditioning until ANC >500.

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Platelet transfusions will be given to maintain the platelet count > 15,000/ L at all times. Single donor platelets will be used with an attempt to use family members when possible. All platelets will be filtered to remove contaminated leukocytes which may harbor cytomegalovirus (CMV). Packed RBC transfusions will be used to keep the hemoglobin level >8.5 gm/dl. All blood products will be irradiated with 2500 cGy prior to transfusion.

The greatest risk for autologous BMT is infection. The management of infections in these immunocompromised patients must by necessity be individualized, but the following general approach will be utilized: If a specific infection is documented, patients will be placed on specific antimicrobial agents to treat that infection. For temperatures > 38.5□ C without an obvious source in patients with less than 1000 granulocytes/1 cultures of blood and urine will be obtained. Following this, a third generation Cephalosporin will be used as initial empiric antibiotic coverage. For persistent or recurrent fevers an amino glycoside and/or Ancef will be added. Prophylactic intravenous Amphotericin B will be used and the dose can be increased as clinically indicated. If a specific organism or site of infection is identified after starting empiric antibiotic coverage, therapy will be changed as needed.

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While hospitalized, patients will have a daily CBC with platelet count, and basic metabolic panel. Comprehensive metabolic panel plus uric acid, LDH, phosphorous determinations will be performed on Monday, Wednesday, and Friday.

During the first year the patient should be seen monthly and have CBC, Diff., platelets, liver function tests and other tests that are clinically indicated. Bone marrow should be performed at day +100 and then yearly for the first two years after the transplant or when clinically indicated.

6.6 Post Transplant Therapy

After PSCT patients will receive Interleukin-2 once the following criteria are met:

A. The patient is less than or equal to 100 days after PSCT and meets the following criteria for peripheral blood.

   i. The patient has an absolute neutrophil count > 500/mm^3 for three days, and

   ii. The patient has a platelet count that can be supported to ≥ 20,000/mm^3 with ≤ one platelet transfusion/day for three days.

B. Patients must have received no growth factors, corticosteroids, pentoxifylline, or amphotericin-B for at least 72 hours.

C. Patients must be afebrile and free of active bacterial, viral or fungal infection.

D. Patients must not be receiving antibacterial, antiviral, or antifungal therapy for fever or a documented infection. Prophylactic antibiotics are allowed.

E. Patients must have a total bilirubin, SGOT, alkaline phosphatase and creatinine ≤ 1.5 x IULN. These tests must be completed within seven days prior to starting treatment.

F. Cardiac: EKG with no evidence of active cardiac disease.

G. Pulmonary: chest x-ray without signs of active pulmonary disease.

   These tests must be completed within seven days prior to starting treatment.

H. Patients must have a KPS of ≥ 70%.

I. Patients must not have mucosal toxicity; not requiring TPN.

6.61 Interleukin-2 (IL-2) Therapy

a). Initiation of IL-2 Therapy

Patients who meet eligibility criteria should begin therapy within three days. Some patients, however, will fail to maintain all eligibility criteria to the initiation of IL-2 therapy. In such cases:

i) IL-2 therapy should be delayed until the patient again meets all of the criteria for IL-2 therapy at which time IL-2 therapy should begin immediately.

ii). Patients who have documented relapse of leukemia as determined by peripheral blood or bone marrow findings will be removed from study and not be treated with IL-2.

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b). Plan of Treatment

i). IL-2 Preparation

Recombinant human IL-2 (Proleukin) manufactured and provided by Chiron-Cetus Corporation will be used in this study. IL-2 activity will be expressed in International Units (IU).

ii). Outline of IL-2 Treatment Regimen

Treatment Phase	Dose	Route	Days	Notes
Course 1 (IL-2 induction)	$9.0x10^6$ $IU/m^2/24hr$	Continuous Infusion	1-4 (total 96hrs)	Requires hospitalization. Begin in AM on Day 1, end in AM on Day 5.
Rest	N/A		5-8	Patient discharged when clinically stable
Course 2 (IL-2 Maintenance)	1.6×10^6 $IU/m^2/24hr$	Continuous Infusion	9-18	Begin in AM on Day 9, ending in AM on Day 19. Administer as outpatient unless hospitalization is clinically indicated.

c) IL-2 Administration

i) IL-2 is administered by continuous intravenous infusion (CIV) through a central venous catheter. Interruptions of the infusion should be limited to no more than 20 minutes per 24 hours.

ii) Induction IL-2 is mixed in 500 cc D5W/day containing 0.1% human serum albumin (HSA) and should be flushed with D5W. The actual volume of each bag containing IL-2 should be determined by the pharmacy in order to calculate the rate to infuse this volume over exactly 24 hours. Failure to do so may result in IL-2 administered for significantly more/less than 96 hours due to overfill/underfill of bags.

iii) Maintenance IL-2 will be administered by CIV via an ambulatory infusion pump, mixed in D5W containing 0.1% HSA, total volume dependent on the particular pump. During maintenance, the IL-2 solution should be changed mid-course.

<u>Formulation/Reconstitution/Storage</u>

IL-2 (Chiron) is supplied as Glyophilized powder. Each 5 cc vial labeled 1 mg, actually contains 1.3 mg of powder. The vial is reconstituted with 1.2 ml of sterile water for injection producing a final concentration of 18 million International Units/mL ($18x10^6$ I.V./ml). Diluent should be directed against the side of vial to avoid excess foaming swirl contents gently completely dissolved. Do not

shake. Since vials contain no preservative, reconstituted solution should be used within 8 hours.

Intact vials are stored in the refrigerator (2-8°C) with protection from light. Each vial bears an expiration date.

6.62 Supportive Care During IL-2 Therapy

a) **Intravenous Fluid Administration**

During induction IL-2 therapy, patients retain sodium and free water and generally exhibit and tolerate weight gain of 5-10% of initial body weight. Aggressive sodium and free water restriction may result in hypotension whereas aggressive sodium and fluid administration may result in pulmonary edema and/or ascites. IV fluid therapy during induction IL-2 should be begun as follows, and adjusted according to the patient's subsequent clinical course:

i) The patient should receive IV hydration with normal saline (NS) at 500 cc/m^2/24 hr.

ii) The patient's total daily IV intake should be limited to $\leq$ 1.5 L/m^2/24 hr.

b) **Prophylactic Antibiotics**

IL-2 causes a reversible defect in neutrophil function. Fevers are almost universal during induction IL-2 therapy and usually do not signify infection. However, gram positive, and rarely gram negative, infections occur in 10-25% of patients. These infections can be serious and, therefore, prophylactic antibiotics should be administered as follows (choice of antibiotics may be altered due to a patient history of sensitivity to these medications). Patients are to receive Levaquin 500mg p.o. q.d. while receiving IL-2.

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c) **Ancillary Medications**

To decrease IL-2 toxicity, the following medications are recommended during IL-2 therapy. Alterations may be made based on individual patient factors. **NOTE:** One dose of acetaminophen, diphenhydramine and naprosyn should be administered prior to each dose of IL-2 during the first week. Then for the subsequent weeks acetminophen should be administered prior to each dose of IL-2. Other medications that could be used for symptom control or prevention are listed below:

i) **Acetaminophen:** 650 mg PO 30 minutes before first dose of IL-2 is administered and q 4-6 hr as needed for fever.

ii) **Diphenhydramine:** 50 mg PO 30 minutes before first dose of IL-2 is administered then 25-50 mg PO or IV q 4-6 hours prn for nausea, pruritis.

iii) **Pepcid:** 20 mg PO or I.V. BID.

iv) **Meperidine:** 25-50 mg IV q 2 hr or 50 to 150mg po prn for chills

v) **Prochlorperazine:** 10mg IV or PO q 6 hr prn for nausea.

vi) **Naproxsyn:** 375 mg PO 30 minutes prior to IL-2, then q 12° for fever/myalgia

vii) **Contraindicated Medications:** See section 6.64

6.63 Supportive Care During Maintenance IL-2 Therapy

During IL-2, most patients can be managed on an outpatient basis. Symptoms of malaise, myalgias and anorexia are common and usually peak toward the end of the maintenance course. Fever is uncommon during maintenance (see Section 6.63.d.i.)

a) IV Fluid Administration is not required unless dictated by inadequate oral intake.

b) Prophylactic Antibiotics:

i) Levofloxacin**:** 500 mg PO qd, (other antibiotics may be substituted based on the individual patient) while taking IL-2.

c) Ancillary Medications:
No other ancillary medications to reduce IL-2 toxicity should be routinely administered during maintenance IL-2 therapy.

i) Tylenol and Indocin should be avoided since they may mask signs of infection

ii) Antiemetics/antidiarrheals/antipuritic agents can be administered as needed on an individual basis.

iii) Contraindicated Medications (see Section 6.64)

d) Toxicity Management:

i) Fever is uncommon during maintenance IL-2 and should strongly suggest a concomitant infection. Patients should

not be treated with antipyretics alone until the potential for infection has been evaluated.

ii) Patients who develop other toxicity(ies) during maintenance IL-2 should be treated according to the guidelines in Section 6.66.

6.64 Contraindicated Medications and Procedures During IL-2 Therapy:

a) **Contraindicated Medications:**

i) Corticosteroids (including any blood product "pre-meds").
ii) Pentoxifylline
iii) IV or IT methotrexate
iv) IV immunoglobulin
v) Other cytokines or growth factors

b) **Radiographic Contrast:**

Ten to twenty percent of patients may develop severe "anaphylactoid" reactions with fever, chills and severe hypotension in response to IV contrast (ionic or non-ionic) administered during or within two weeks of completing IL-2 therapy. IV contrast administration (ionic or non-ionic) should, therefore, be avoided unless clinically necessary during these times.

6.65 Dose Modification during IL-2 Therapy

a) Treatment with IL-2 is continued until completed or until Grade 3 or 4 toxicity (or Grade 2 neurologic or cardiac toxicity; Grade 4 neutrophils or bilirubin; or platelets < 10,000/mm^3 with transfusions) occurs at which time IL-2 is discontinued until a return to Grade 1 toxicity, at which time IL-2 therapy will be resumed at 50% of the initial dose. If Grade 3 or 4 toxicity, or Grade 2 neurotoxicity or cardiac toxicity, recurs after resumption of the reduced dose of IL-2 then IL-2 is discontinued and not restarted.

b) Reduction or discontinuation of IL-2 therapy due to toxicity does not alter the IL-2 treatment schema (Section 6.61.b.ii). If temporarily interrupted, IL-2 therapy is resumed according to the day of the original schedule. Any doses missed due to toxicity are not administered, and total duration of therapy is not extended beyond the original plan at initiation of IL-2 therapy.

6.66 Toxicities of IL-2 Therapy

a) High-dose IL-2 administered by CIV results in dose and time dependent toxicities which peak toward the end of the induction course. The most common clinical toxicities seen during induction

IL-2 are of a flu-like syndrome with fever, chills, weight gain, nausea, diarrhea, and rash.

b) Capillary Leak Syndrome (CLS): The CLS is characterized by peripheral of pulmonary interstitial edema and/or ascites, and "sepsis-like" physiology, i.e., decreased systemic vascular resistance and increased cardiac output. Dose modifications are made for specific organ system toxicity, as per Section 6.65.

c) Hypotension: Mild hypotension with systolic blood pressure (SBP) 10-20% below baseline is common in patients receiving induction IL-2.

i) Asymptomatic patients with SBP > 90 mm Hg should be monitored closely.

ii) Any symptomatic patient (regardless of the SBP) and all patients with SBP $\leq$ 85 mm/Hg should be treated immediately with a fluid bolus of NS, 5-7 ml/kg (STAT x 1-2) which may be supplemented with red cell transfusions or colloid infusion. Hypotension which does not respond to fluid therapy should be treated with low-dose dopamine or a phenylephrine infusion, and IL-2 therapy should be interrupted until hypotension resolves.

iii) Grade 3 hypotension which does not respond to crystalloid/colloid therapy requires:

IV pressors, preferably phenylephrine (rather than dopamine).

Discontinuing IL-2 infusion

d) **Arrhythmias:**

i) Sinus Tachycardia: is common, especially during fever, and is not an indication for intervention.

ii) Supraventricular Tachycardia: Occurs in < 10% of adult patients and is an indication to discontinue IL-2 until SVT resolves. If patient is hemodynamically unstable, this shouldbe treated with Digoxin or cardioversion **NOT** verapamil (which may result in severe hypotension)

e) **Renal Dysfunction:** Most patients will develop oliguria and some elevation of serum creatinine ($\leq$ 2.0 x baseline) during induction IL-2 due to decreased renal perfusion, intrinsic renal effects of IL-2 and indomethacin. This is usually quickly reversible after induction IL-2 is completed.

i) The common manifestations of IL-2 induced renal dysfunction are:

Weight gain of 1-10% of baseline body weight.
Metabolic acidosis (total CO 15-20).
Lowering of serum K+, Mg++, Phos+.

ii) During induction IL-2 therapy, these guidelines should be followed:

a. Allow the patients to gain $\leq$ 1-1.5%/day of baseline body weight.

b. Reserve diuretic therapy for patients with symptomatic interstitial edema (i.e.,pulmonary edema, or ascites). Overly aggressive diuresis for asymptomatic patients with weight gain and oliguria will often result in hypotension and worsening of renal dysfuntion.

c. If creatinine increases by < 50% over baseline, reduce indomethacin to q 12 hr.

d. If creatinine increases by $\geq$ 50% over baseline, discontinue indomethacin.

e) **Hematologic Side Effects – Background**:

IL-2 therapy causes the following hematologic effects.

i) **Lymphocytosis** as high as 20-50,000/mm^3 occurs often and is maximal 24 hours after stopping induction IL-2; lymphopenia occurs during Days 1-4 of induction IL-2.

ii) **Anemia** occurs often, due to decreased production and destruction RBC's. Most patients will require RBC transfusions during induction IL-2.

iii) **Neutrophilia and Eosinohilia** occurs often, and is due to secondary release of GM-CSF,IL-5 and IL-3.

iv) **Thrombocytopenia** occurs often. Platelet counts are lowest on Days 4-9 of IL-2 therapy, and most patients will require more frequent platelet transfusions during this period.

g) **Infectious Complications**:

i) All patients should receive prophylactic antibiotics during induction IL-2.

ii) Blood cultures should be drawn at least once per day for temperature spikes.

iii) Any fever that persists more than 24 hours after induction IL-2 is completed should suggest a secondary infection and **NOT** be ascribed to IL-2 until infection has been ruled out.

h) **Gastrointestinal Toxicity**:

Nausea, vomiting and diarrhea are common during induction IL-2. Most patients have a limited oral intake during this time. These symptoms usually improve quickly once IL-2 is discontinued.

i) **Hepatic Toxicity**:

i) Cholestasis with elevated bilirubin and alkaline phosphatase is common, usually peaks on Day 5-7 and quickly resolves.

ii) Drugs which are hepatically metabolized may need temporary dose reductions during this period of hepatic dysfuntion.

j) **Neurologic Toxicity**:

i) Neurologic abnormalities such as lethargy, mild confusion, subtle personality change and memory disturbance occur in some patients receiving narcotics, sedatives or antiemetics concomitantly with IL-2. Patients with these symptoms should have psychoactive drugs reduced or discontinued.

ii) In any patient who develops $\geq$ Grade 2 neurologic toxicity, IL-2 will be discontinued immediately and permanently.

7.0 **COMPLICATIONS OF THERAPY**:

Busulfan: Human toxicity from busulfan includes: a) Severe bone marrow hypoplasia which could be fatal without administration of bone marrow or peripheral blood stem cells. b) Nausea and vomiting which can be decreased by the use of sedation and antiemetics. c) Stomatitis and diarrhea which can be treated symptomatically with fluid replacement and atropine or diphenoxylate Hcl. d) Pulmonary fibrosis chara-cterized by delayed onset of cough, shortness of breath and low grade fever. e) Hepatic damage which can occur in combination with melphalan 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.

Total body irradiation: The short term and long term complications of TBI have been reviewed by others. Most patients will experience nausea and vomiting. This problem will be managed symptomatically and usually resolves within 24 hours of ending therapy. Oral mucositis is expected in virtually all patients. Mouth care will be performed with hydrogen peroxide ad clotrimazole. Only toothbrushes will be allowed. Pain will be managed with morphine or dilaudid. All patients should expect permanent sterility. It is probable that most patients will be infertile from previous therapy, but male patients will be offered the option of semen storage before therapy. Temporary alopecia will also be expected in all patients. Long term survivors may develop cataracts within a few years following BMT. These can be managed successfully in the same way as cataracts, unrelated to radiation. Solid tumors have been seen following TBI. Radiation fibrosis of the lung and hypothyroidism are also potential but unlikely complications.

Autologous PSC Reinfusion: Side effects from the bone marrow and peripheral stem cell infusion should be minimal. Volume overload may be seen, but can be managed with diuretics. Fevers and chills may occasionally be encountered. At the University of Nebraska at least two patients developed acute abdominal pain of unknown cause during their marrow infusions. The pain was managed with narcotic analgesics and resolved spontaneously. The lysis of frozen erythrocytes may be associated with hemoglobinuria. Patients will have positive tests for blood in the urine, but no erythrocytes will be found in the sediment. At the University of Nebraska three patients developed acute renal failure after autologous bone marrow infusion. This problem was presumed to be due to hemoglobinuria and was no longer seen after red blood cells were removed from the marrow prior to cryopreservation. This is not expected to be a problem since we will also be removing the red cells with Ficoll-Hypaque. DMSO will be infused along with the bone marrow. It is excreted through the lungs and its characteristic odor may be noticeable for a few days after marrow infusion.

8.0 **STATISTICAL CONSIDERATIONS**:

8.1 Primary and Secondary Endpoints: The primary endpoints of this Phase II study are to evaluate the toxicity and efficacy of FTBI/VP-16 and targeted Busulfan dosage for AUC 700-900 as a preparative regimen for autologous BMT with primed peripheral stem cells following consolidation therapy with high dose Ara-c and idarubicin or high dose Ara-c alone in patients with AML in first complete remission (CR). Complete remission will be defined as neutrophils >1500/ml and platelets >100,000. Efficacy will be estimated as 2 and 5 year disease-free survival (DFS). The role of IL-2 following autologous BMT will also be evaluated based on feasibility of administration and ability to tolerate IL-2. The effect of cytogenetics, WBC at presentation, AUC of Busulfan and number of courses of induction therapy to achieve remission will be evaluated as possible prognostic factors for relapse, DFS, and overall survival.

8.2 Sample Size Estimation and Length of Accrual: A total of 50 patients with AML in first CR and less than $\leq$ 60 years old will be accrued to this trial, so that in estimating the engraftment and relapse rates the maximum standard error will be 0.07. We expect to accrue approximately 10-12 patients per year so that this trial will require 4-5 years for completion.

8.3 Statistical Analyses: The rate of engraftment and median time to engraftment will be estimated, defined as time to ANC>500 and platelets > 20,000.

The Kaplan-Meier method will be used to estimate time to relapse, DFS, and overall survival, and 95% confidence intervals will be calculated using Greenwold's variance. All patients receiving HD Ara-c and Idarubicin consolidation will be included in the analysis for intent-to-treat with autologous BMT. For overall survival, failure time will be calculated from the day of first consolidation treatment to the day of death due to any cause for those patients who fail. For DFS, the failure time will be calculated from the day of first treatment to the day of disease relapse or death due to any cause. For patients who remain alive and well at the time of analysis, the survival time will be censored as of the date of last contact.

A further analysis of time to relapse, DFS and overall survival will be carried out for the subset of patients who go on to autologous BMT, with survival estimates calculated from the day of transplant. The Cox proportional hazard regression model will be used to analyze possible prognostic factors for relapse, DFS and overall survival.

8.4 Early Stopping Rules: If at any time the severe treatment related complication rate (e.g. severe VOD, interstitial pneumonia, neurotoxicity at day 100 post ABMT), exceeds 10%, with a high probability (i.e. 95%) then further accrual to the trial will be terminated. Similarly if with a high probability (95%) the regimen related mortality at day 100 post ABMT exceeds 10% the trial will be terminated. This would occur if the following numbers of events have been observed, monitoring after every set of 10 patients it accrued:

Number of Patients Accrued	Number of Adverse Events Leading to Early Termination
10	4
20	5
30	7
40	8

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We will stop accrual of good risk cytogenetic patients on the study if the good risk cytogenetic patients demonstrate excess relapse. Based on previous COH experience, good risk cytogenetic patients have a relapse rate of 13%. The study will close if the lower bound of an estimate of the true rate of relapse exceeds 15% for the subgroup. Evidence of relapse will be taken as the lower limit associated with an exact 95% one-sided confidence interval for proportions. Table 1 below shows the critical points for early stopping of accrual.

Table 1: Critical points for early stopping for relapse

Critical points for early stopping	95% one-sided CI
Cumulative enrollment of good risk cytogenetic patients	Conclude omitting idarubicin poses a safety threat in >15% of pts if N experiencing relapse is at least:
5	3
10	4
15	6
20	7

25	8
30	9
35	10

9.0 WOMAN 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 population and previous experience with bone marrow transplantation for AML in first remission, the anticipated rates of entry into this study by gender and race/ethnicity are as follows:

Gender/Race/Ethnicity Table for Acute Myelogenous Leukemia Patients in First Complete Remission Transplanted at City of Hope National Medical Center

	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%	12%	2%	16%	70%	0%
Male	0%	8%	2%	22%	65%	3%
Total	0%	10%	2%	19%	65%	2%

10.0 REGISTRATION GUIDELINES:

Once signed, informed consent has been obtained and all pretreatment evaluations have been performed, patients will be entered on study, after review of patient eligibility criteria by the assigned Clinical Research Associate (CRA) from City of Hope Department of Biostatistics. Patients may be screened for registration by calling the Department of Biostatistics, ext. 63811. Eligibility checklists are attached. (Appendix IX). Patients will be taken off study at time of death.

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11.0 DATA SUBMISSION SCHEDULE:

All primary data will be maintained by the assigned CRA from the Department of Biostatistics. 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.

Rev. 3/11/02 See Appendix VIII for time points for grading toxicities.

12.0 ETHICAL AND REGULATORY CONSIDERATIONS:

This study is to be approved by the Institutional Review Board 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 meeting, identification of those taking part will be withheld. Medical Records of patients will be maintained in strictest confidence, according to current legal requirements. However, they 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.

13.0 Data & Safety Monitoring Plan (See Appendix VII)

Toxicities will be graded using the Common Toxicity Criteria 2.0 published date April 30, 1999, Appendix VI [special attention to BMT section].

Frequency for grading and recording toxicities, see Appendix VIII.

i. The COH IRB and the Clinical Protocol Review Monitoring Committee (CPRMC) and Data Safety Monitoring Board (DSMB) will have the data monitoring oversight responsibilities. The COH has an NCI approved clinical monitoring plan. The CPRMC is an NCI approved clinical trials monitoring committee. The COH IRB meets twice monthly and reviews protocols annually. The CPRMC meets twice per month. Monitoring accrual and SAE's will be performed by that committee. Adverse events will be reported to the COH IRB and CPRMC [DSMB].\

ii. Guidelines for reporting AE's and ADRS – See Appendix VII.

14.0 REFERENCES

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Appendix I

IV BUSULFAN KINETICS FORM

IRB#: _____ DATE: _____

PATIENT _____ DOSE #_____ Actual Body Weight _____

Medical Record #_____ Start time: _____ Stop time: _____

Date of birth: _____ DOSE: _____mg

Social Security#: _____ MD/Pager#: _____ Coordinator/Pager #_____

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 _____

Ship on 5kg dry ice.
Results will be reported to the attending physician page by 4 p.m. Pacific time.
Results will also be faxed.

Revised 3/11/02

Appendix II

COH Schema

Session	Day	Time	Beam Direction	Energy (MeV)	Dose (cGy)	Notes
1	–6	0730	AP	8/10X	120	TLD
2	–6	1230	PA	8/10X	120	
3	–6	1730	AP	8/10X	120	
4	–5	0730	PA	8/10X e^- boost	120x 300e^-	Chest-wall boost need not be given in successive fractions
5	–5	1230	AP	8/10X e^- boost	120x 300e^-	
6	–5	1730	PA	8/10X e^- boost	120X 300e^-	
7	–4	0730	AP	8/10X e^- boost	120X 300e^-	
8	–4	1230	PA	8/10X	120	
9	–4	1730	AP	8/10X	120	
10	–3	0730	PA	8/10X	120	

Appendix IIa

University of Wisconsin Hospital and Clinical TBI Schema
BMT 2001-403 UWHC
IRB# 99040

Session	Day	Time	Beam Direction	Energy (MeV)	Dose (cGy)	Notes
1	–6	0730	AP	8/10X	150X	TLD
2	–6	1700	PA	8/10X	150X	
3	–5	0730	AP	8/10X e^- boost	150X, 300 e^-	
4	–5	1700	PA	8/10X e^- boost	150X, 300 e^-	
5	–4	0730	AP	8/10X e^- boost	150X, 300 e^-	
6	–4	1700	PA	8/10X e^- boost	150X, 300 e^-	
7	–3	0730	AP	8/10X	150X	
8	–3	1700	PA	8/10X	150X	

Electron beam set so the 90% PDD fails at the pleura.

2/26/02 written by Bruce Thomadsen, Physicist
Department of Radiation Oncology
University of Wisconsin Hospital and Clinics

Revised 8/7/00
Rev. 1/30/01
Rev. 3/19/02

Appendix III

Consolidation therapy (All testing to be completed no more than 4 weeks prior to starting treatment)

Required studies	Pre study	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 15	Until PBSC
BM asp, biopsy	X														
Cytogenetics	X														
HIV	X														
CBC,Diff, PLT **	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CMP, uric acid, phosphorous, LDH ++	X	X		X		X		X		X					
Magnesium ++	X	X		X		X		X		X		X		X	
UA	X														
24hr Crea cl	X														
Hepititis panel	X														
Herpes simplex titer	X														
CMV titer	X														
Immunogloblobulin levels	X														
Thyroid panel	X														
CXR	X														
LP*	X														
ECHO or MUGA	X														
CT scan Chest, ABD, Pelvis	X														
PFT	X														
HLA Typing of patient and sibling	X														
Pregnancy	X														
Cholesterol	X														
TREATMENT															
Consolidation															
HD ARA-C		X	X	X	X										
Idarubicin***		X	X	X											
GCSF#													X	X	X

*Lumbar Puncture will be performed in patients with FAB M4, M4eo, M5, and patients with WBC at diagnosis >50,000 and patients with cutaneous involvement 12 mg of intrathecal methotrexate should be given at the time of the LP.

GCSF will be given until stem cells are collected

++ Comprehensive Metabolic Panel plus uric acid, phosphorous and LDH every Monday, Wednesday, Friday during consolidation

** CBC, Diff, PLT should be done until ANC >1500 and PLTs >150. Diff. to be done on admission and then when WBC recovers to >500.

***Give Idarubicin dose after Ara-C dose 1,3 and 5.

See section 6.1 for exceptions.

++Comprehensive Metabolic Panel [See appendix X for tests included].

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Rev. 11/7/01

Appendix IV
HD Therapy/Transplant therapy

Required studies	Pre treatment	Day -17	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 0	Day 1	Day 2	Day 3	Day 4	Day 100	Yearly X 2 years
Busulfan PK			X		X	X															
CBC,Diff, PLT*	X		X		X	X			X	X	X	X	X	X	X	X	X	X	X	X	X
Basic MP $	X		X		X	X			X	X	X	X	X	X	X	X	X	X	X	X	X
CMP++	X					X			X					X		X		X		X	X
MG ++	X					X								X			X				
PT,PTT	X																				
UA	X																				
24hr Crea cl *	X																				
PFT *	X																				
EKG	X																				
CXR	X																				
CT Scan Chest, ABD	X																				
ECHO or MUGA	X																				
BM asp, bx, cytogenetics	X																			X	X
Dilantin level			X		X																
Busulfan blood Shipment			X		X																
TREATMENT																					
Dilantin +++		X	X	X	X	X	X	X	X	X		X									
Busulfan			X		X	X	X	X	X												
TBI										X	X	X	X								
VP-16														X							
CNS Disease patients see section 6.53																					

*As clinically indicated
++ Every Monday, Wednesday, Friday during hospitalization
** CBC, Diff, PLT should be done daily until ANC >1000 and PLTs >50 and then at physicians discretion
See section 6.1 for exceptions
+++Dilantin given day –17 to Day –4
+ Day –11 labs done only if 2nd test dose of Busulfan given.
***Busulfan pharmokinetics done on day –13.
Busulfan pharmokinetics done on day –11 only if dose adjustment needed.
Busulfan pharmokinetics done on day –10 only if dose adjusted.
$ Basic MP see Appendix X

Appendix V

Post BMT Therapy/ IL2 therapy (All testing to be completed no more than 7 days prior to starting treatment)

Required studies	Pre IL-2	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 14	Day 19	Annually X 2 years
CBC,Diff, PLT	X	X	X	X	X	X				X	X	X	X
CMP	X	X		X		X				X	X	X	X
Magnesium ++	X	X		X		X				X		X	
EKG	X												
CXR	X												
BM asp,bx cytogenetics													X
TREATMENT													
Course 1* IL2 Induction		X	X	X	X	~~X~~							
REST						X	X	X	X				
Course 2** IL2 maintenance										X	thru	X	
Toxicity notation		X	X	X	X	X	X	X	X	X		X	X

*IL-2 96 hr infusion

** IL-2 maintenance 10 day infusion.

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