Treatment of Elderly AML Patients with Induction Chemotherapy followed by G-CSF-Mobilized Stem Cells from Haploidentical Related Donors

PROTOCOL FACE
MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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Table of Contents

1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is a single center trial of induction chemotherapy followed by a single dose of unmanipulated donor-derived GCSF-mobilized peripheral blood stem cells (G-PBSC) for the treatment of elderly patients with acute myeloid leukemia (AML). Patients older than 60 years of age with newly diagnosed disease will be eligible. Selection of haploidentical related donors will be based on KIR/HLA genotypes to maximize missing self-MHC, anti-tumor, and anti-GVHD NK activity. No drug prophylaxis against GVHD will be administered following G-PBSC infusion. The primary objective will be to assess the feasibility of delivering this treatment in terms of timely HLA/KIR typing, donor selection, pheresis procedure, and infusion of stem cell product. The target accrual is 15 patients in 18 months. Secondary objectives will be to determine the anti-leukemic effects (in terms of CR rate), reduction of cytopenia-related toxicity (infection, bleeding, duration of hospital stay), and toxicity of treatment (GVHD) of this therapy in elderly AML patients and to correlate response to KIR and HLA genotyping and NK function. Correlative studies will assess NK activity against standard target cells *in vitro*, donor NK activity against AML blasts, donor-host chimerism, and immune reconstitution.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

2.1 Primary objective:

- To assess the feasibility of rapid donor selection, pheresis, and stem cell infusion for AML patients undergoing induction chemotherapy. The first objective is to enroll and to treat 15 patients in 18 months.

2.2 Secondary objectives:

2.2.1 Clinical Outcomes

- Rate of achievement of CR
- Duration of neutropenia and thrombocytopenia
- Treatment Related Mortality (TRM)
- Graft versus Host Disease (GVHD)
- Severe (CTCAE v4.0 grade 4-5) infection
- Donor chimerism >5% at 100 days
- Likelihood of patients to be enrolled and to receive treatment
- Duration of hospital stay

2.2.2 Correlative studies

- To assess lymphocyte reconstitution: NK, T, and B

3.0 BACKGROUND AND RATIONALE

Acute myeloid leukemia (AML) is a malignancy that results in an accumulation of leukemic blasts and ineffective hematopoiesis producing varying degrees of thrombocytopenia,

anemia, and neutropenia. The incidence of AML increases with age, with a median age at diagnosis of 67 years.[1] Of the almost 13,000 patients diagnosed annually, there will be an estimated 9000 deaths attributable to AML.[2] A 60-80% complete remission rate (CR) is reported for younger adults whereas only 40% of older adults enter CR, and <10% are long-term survivors.[3]

AML in older adults is often preceded by myelodysplastic syndrome (MDS) or myeloproliferative disorders, has an increased incidence of poor-risk cytogenetics, more frequently expresses multidrug resistence and has a lower response rate to chemotherapy. There is a significant difference in biology of AML in older adults along with an increase in co-morbid diseases and impaired bone marrow stem cell reserves, resulting in an extremely poor overall prognosis.[3, 4]

There is a significant need for more effective therapy in elderly patients with AML, as standard chemotherapy results in poor outcomes that have not changed for the past 30 years. Allogeneic stem cell transplantation (allo SCT) after nonmyeloablative or reduced intensity conditioning (RIC) has been shown to offer an improvement in outcome of elderly patients with AML. However, there are several major obstacles to the more widespread use of allogeneic transplant in this population: First, the number of persons who achieve an adequate remission for allo SCT is rare; second many persons lack a human leukocyte antigen (HLA)–matched donor, finally, increased treatment-related mortality (TRM) in elderly persons from prolonged marrow aplasia and graft-*versus*-host disease (GVHD) means that only the fittest patients are referred for allo SCT. This limits the utility of allo SCT in elderly patients because of their often poor performance status and increased comorbidities. [5-7]

Clinical and pre-clinical studies demonstrate that G-CSF–mobilized donor peripheral blood stem cell (G-PBSC) infusion results in a graft-*versus*-leukemia effect and hastens hematologic recovery.[5, 8, 9] Mice infused with a high dose of G-CSF–mobilized allogeneic spleen cells (3-12 x 10^7) after cytarabine chemotherapy and without immunosuppressive pretreatment exhibited rapid autologous hematopoietic recovery and persistent microchimerism without GVHD. This led to a recent clinical control study to investigate the effects of conventional chemotherapy combined with G-PBSC infusion on outcomes of AML in elderly patients.[10] In this study, patients received conventional chemotherapy (cytarabine and mitoxantrone) followed 36 hours later by G-CSF mobilized PBSC from an HLA-haploidentical related donor. The median numbers of $CD34^+$, $CD3^+$, $CD3^-CD16^+CD56^+$ and $CD3^+CD16^+CD56^+$ cells infused per course were 1.7 (1.1-4.6) x 10^6/kg, 0.9 (0.5-2.6) x 10^8/kg, 0.19 (0.075-0.25) x 10^8/kg and 0.13 (0.05-0.45) x 10^8/kg, respectively. Patients receiving combination chemotherapy (induction and consolidation chemotherapies) and G-PBSC achieved a higher CR rate (80%) and 2-year probability of disease-free survival (39.2%) compared with patients receiving conventional chemotherapy alone (42.8% and 10%). The median recovery time of neutrophils and platelets was shorter in the G-PBSC group compared with the control group with first cycle of induction chemotherapy (11 and 14.5 days versus 16 and 20 days from donor cell infusion). All pts received GCSF upon neutropenia. The severe infection rate with first induction was lower in the G-PBSC group (26.7% vs. 57.1%). These findings demonstrate the potential of G-PBSCs in combination with conventional chemotherapy in improving the outcome of AML in elderly patients. In an expansion paper, Guo et al treated an additional 101 patients with G-PBSC following induction therapy for AML.[11] Both in this cohort and the original case-control series there

were no reported incidences of acute or chronic GVHD. Chimerism studies here demonstrated persistent microchimerism ($<10^{-5}$ to 10^{-4}) for 0.5-34 months in most persons tested. A third study further demonstrated the safety of infusing allogeneic stem cells with as many as $1x10^8$ CD3/kg into 13 minimally pre-treated patients without evidence of engraftment of development of GVHD.[12] Chimerism and/or GVHD with donor lymphocyte infusions containing up to $6.85x10^8$ mononuclear cells/kg and $1.9x10^8$ CD3/kg, even with fairly minimal conditioning, has occurred, but only in patients who were heavily pre-treated, including those with a prior autologous stem cell transplantation.[13, 14] Taken together, these studies suggest that haploidentical G-PBSC retains a graft *versus* leukemia effect despite non-engraftment. Furthermore, patients who are minimally pretreated can receive a stem cell infusion containing T-cells of 1 $x10^8$/kg without significant risk of GVHD.

In the Guo study, the decreased time to hematopoietic recovery in patients who received G-PBSC after chemotherapy was associated with a profound decrease in infectious complications, thereby reducing the high morbidity and mortality rates associated with induction chemotherapy in the elderly. It is known that PBSC therapy can significantly speed hematopoietic recovery after chemotherapy, thereby reducing treatment-related morbidity and mortality. In 1958, a radiation accident at a nuclear power plant in Vinca, Yugoslavia resulted in radiation poisoning to 6 workers, one of whom died from prolonged aplasia.[15, 16] Unrelated individuals donated bone marrow to the remaining 5 stricken workers, all of whom recovered autologous hematopoiesis after brief allo-engraftment without GvHD. It was universally accepted that without the aid of stem cell infusion, these individuals would also have died due to prolonged aplasia. At least two other modern applications of “cell-assisted” marrow recovery currently exist in transplant medicine, where the infusion of two umbilical cord allografts allows faster engraftment of one, and where infusion of haploidentical stem cells assists in the rapid engraftment of a single cord allograft.[17-19] Hastened engraftment leads to lower infectious and bleeding complications, without engraftment or GvHD from the “enabling” stem cell graft. Furthermore, the reduced neutropenic period leads to shorter hospitalization.

Another factor contributing to the positive findings is an enhanced antileukemic effect mediated by the G-PBSC, leading to a higher rate of CR. While anti-leukemic alloactivities in DLI have been well demonstrated, these are primarily mediated by long-lived T-cells with specificity for host leukemic antigens.[13, 20-22] A more intriguing prospect is that the higher anti-leukemic effect is mediated by donor alloreactive NK cells. Several features of NK cells support this possibility: 1) NK cells have inherent anti-tumor effects and therefore “naïve” NK cells can mediate tumor eradication immediately upon infusion or development from stem cells; 2) NK cells are the first lymphocyte to develop from the stem cell and to populate the periphery following allogeneic stem cell transplantation; therefore, given the lack of sustained allo-engraftment seen in the recipients, the only donor-derived cell that could mediate short-term anti-leukemic effects is the donor NK cell; 3) HLA-mismatched NK cells have a high likelihood of becoming alloreactive due to missing self-HLA ligands in the recipient.[23]

On the basis of the two Guo trials and prior observation of the safety of infusion HLA-mismatched stem cells into non-heavily pre-treated patients our trial will assess the feasibility and efficacy of combining a standard induction chemotherapy regimen of daunorubicin and

cytarabine (7+3 scheme) with the infusion of unmanipulated G-PBSC from a haploidentical related donor, for elderly patients (>60 years old) with newly-diagnosed AML. The majority of patients are expected to have an eligible haploidentical donor, but in contrast to the previously reported study, donor selection will be based on KIR/HLA genotypes. This will be done to maximize the likelihood of NK alloreactivity due to missing self-MHC, to enhance NK activity due to activating KIR, and, subsequently, to maximize anti-leukemic potential.

Previous studies have shown the feasibility and safety of NK infusion in patients affected by hematological (AML) and non-hematological diseases. In all of these previous experiences no GVHD has been documented.[24, 25] To maximize in vivo donor NK survival and alloreactivity, related but HLA-disparate donors are screened and prioritized based on KIR/HLA genotypes. To maximize NK activation due to "missing self," selection will be prioritized for donors exhibiting KIR ligands that are lacking in the patient. Cognate inhibitory KIR in the donor is confirmed by KIR genotyping. To capture KIR2DS1-mediated NK activation, donors with activating KIR2DS1 are then prioritized if the donor exhibits an HLA-C1 allele. Donors who are KIR-ligand matched to the recipient are acceptable if KIR typing indicates that the recipient lacks class I ligand for the donor inhibitory KIR, leading to activation of unlicensed NK cells. Donors lacking class I ligands present in the recipient are less desirable, as this may result in rapid clearance of the infused product by residual host NK cells. Based on HLA and KIR genotype frequencies in the Caucasian population: 1) 40% of patients will have all KIR ligands present and will not benefit from missing self or missing ligand NK alloreactivity; 2) 60% will benefit from missing ligand; and in overlapping groups, 3) approximately 24% will benefit from "missing self" donor alloreactivity; and 4) 32% of patients will benefit from KIR2DS1-mediated NK activity.[26-29]

It is recognized that some of the patients who receive this therapy and achieve CR will be eligible for a standard allogeneic hematopoietic cell transplant (HCT) and that a fraction of these patients may have a fully HLA-matched sibling donor. Allosensitization from prior exposure to blood products from family members can predispose to stem cell allograft rejection. The goal of this trial, however, is to successfully achieve higher rates of sustained CR. Assuming that this is accomplished to the same degree as published, twice as many patients will achieve CR and will therefore be eligible for allogeneic HCT. Of these, however, only a portion will undergo HCT, and of this portion, only 25% will have an HLA-identical sibling. Therefore, it is the determination of both the Leukemia and the Adult Allogeneic Bone Marrow Transplantation Services that the risk of HCT graft rejection due to allosensitization should not preclude pursuing the proposed treatment plan. Furthermore, at present most of these patients will receive a T-replete, unmodified cell allograft. The risk of graft rejection with this type of allograft is <5%.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a pilot study designed to assess the feasibility and to estimate the efficacy of standard induction chemotherapy followed by a single dose of unmanipulated G-CSF mobilized haploidentical peripheral blood stem cells for the treatment of newly diagnosed elderly AML patients.

The study will use a two-step enrollment process. First, patients eligible for this study will be enrolled. Second, the donors are HLA and KIR genotyped to determine if they are appropriately mismatched and are willing to participate in the study. The feasibility objective will examine whether a sufficient percentage of prospective patients that are enrolled in this protocol undergo the stem cell infusion. Patients declared eligible will be enrolled. Feasibility will be determined by the number of patients who receive treatment. Treatment will consist of one cycle of standard induction chemotherapy followed by infusion of haploidentical G-PBSC. An additional cycle of consolidation with haploidentical G-PBSC infusion is allowed at the investigator's discretion. It is anticipated that 15 patients will be treated within 18 months. Patients enrolled who do not proceed to stem cell infusion due to donor unavailability or ineligibility will be removed from the protocol and treated with standard chemotherapy. The efficacy objective will provide pilot data for the response rate, as defined by achievement of CR.

Secondary outcomes evaluated will be: Rate of achievement of CR, duration of neutropenia and thrombocytopenia, incidence of TRM, GVHD, and severe infections; donor cell chimerism at 100 days <5%; NK immunogenetics and CR; duration of hospital stay during induction therapy. Correlative studies will assess NK activity against standard target cells in vitro, immune reconstitution (NK, T, B) and, if AML blasts available, donor NK activity against tumor targets.

4.2 Intervention

Donor intervention:

G-CSF mobilized PBSC will be collected according to standard protocol. Donors will receive filgrastim 10 µg/kg/day subcutaneously x 5 days and then undergo 1day of apheresis using standard protocol on days 5±6.

Patient intervention:

Elderly patients (>60 y) with a new diagnosis of AML will receive a standard induction chemotherapy with daunorubicin and cytarabine (7+3 scheme) followed by infusion of unmanipulated G-PBSC from a haploidentical related donor.

The treatment plan for the patients receiving 7+3 chemotherapy is outlined below:

DAY	1	2	3	4	5	6	7	8	9-11
Cytarabine (100 mg/m^2 IVCI)	X	X	X	X	X	X	X	rest	G-PBSC infusion
Daunorubicin (60 mg/m^2 IVP)	X	X	X						

Due to variability in donor availability and/or pheresis scheduling, patients may receive the G-PBSC up to 84 hrs after completion of chemotherapy. The dose of the GCSF-mobilized PBSC allograft will be capped so as not to exceed a CD34 count of 2x10e6/kg or a CD3+

count of 1x10e8/kg. Remaining donor G-PBSC after the initial infusion may be cryopreserved.

Some patients will require additional consolidation chemotherapy. This study allows G-PBSC to be infused after the first cycle of consolidation. To minimize the potential for persistent donor cell macro-engraftment G-PBSC will only be used after the first cycle of consolidation. Additional cycles of consolidation may be used at the investigator's discretion without G-PBSC. Patients requiring treatment for relapse will not receive G-PBSC. The treatment plan for consolidation is below:

DAY	1	2	3	4	5	6	7-9
Cytarabine 1.5-3 g/m^2/BID	X		X		X		G-PBSC infusion

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 DAUNOrubicin (Daunomycin, Cerubidine®)

Daunorubicin hydrochloride is the hydrochloride salt of an anthracycline cytotoxic antibiotic produced by a strain of *Streptomyces coeruleorubidus*. Daunorubicin has antimitotic and cytotoxic activity through a number of proposed mechanisms of action. Daunorubicin forms complexes with DNA by intercalation between base pairs. It inhibits topoisomerase II activity by stabilizing the DNA topoisomerase II complex, preventing the religation portion of the ligation-religation reaction that topoisomerase II catalyzes. Single strand and double strand DNA breaks result. Daunorubicin hydrochloride may also inhibit polymerase activity, affect regulation of gene expression and produce free radical damage to DNA. In the treatment of adult acute nonlymphocytic leukemia, daunorubicin hydrochloride, used as a single agent, has produced complete remission rates of 40 to 50%, and in combination with cytarabine, has produced complete remission rates of 53 to 70%.

The contents of the 50 mg vial should be reconstituted with 10 mL of Sterile Water for Injection, USP, and agitated gently until the material has completely dissolved. The sterile vial contents provide 50 mg of daunorubicin, with 5 mg of daunorubicin per mL. The desired dose is withdrawn into a syringe containing 10 mL to 15 mL of 0.9% Sodium Chloride Injection, USP and then injected into the tubing or sidearm in a rapidly flowing IV infusion of 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP. Daunorubicin hydrochloride should not be administered mixed with other drugs or heparin. Unopened vials of daunorubicin must be stored per package label refrigerated at 2° to 8°C (36° to 46°F). Store prepared solution for infusion at 15° to 30°C (59° to 86°F) for up to 24 hours. Solution contains no preservative and must be protected from light.

Daunorubicin will be administered intravenously at a dose of 60mg/m^2 daily for 3 days. It will be administered as an IVP.

5.2 Cytarabine (Ara-C®)

Cytarabine is a pyrimidine nucleoside analogue that is one of the most widely employed and effective drugs for the treatment of AML. It acts by inhibiting DNA polymerase and promoting DNA chain termination through the ability of its phosphorylated metabolite, ara-CTP, to incorporate into DNA. The most important catabolic step in the metabolism of cytarabine is its conversion to an inactive intermediate, ara-U, by a deaminase. Resistance to the drug appears to occur through a variety of mechanisms including poor cellular uptake, deletion of the activating enzyme, altered DNA affinity, and high levels of dCTP, a normal competitive inhibitor.

Cytarabine is supplied as a sterile powder in 100 mg and 500 mg vials. The drug is reconstituted with bacteriostatic water (without benzyl alcohol) for injection. The resulting solution contains 50 mg/mL of cytarabine. It may be stored at room temperature for 48 hours. The drug may be administered intravenously, subcutaneously, or intrathecally. When given intravenously at standard doses of 100-200 mg/m^2, cytarabine is generally administered by continuous infusion over 24 hours. At higher doses (1-3 gm/m^2), it is administered intravenously over 1-3 hours.
Cytarabine will be administered at a dose of 100 mg/m^2/day by continuous IV infusion (Days 1-7).

5.3 Filgrastim (G-CSF, Neupogen®), for donor

Granulocyte colony stimulating factor (G-CSF) is one member of a family of glycoproteins that are important in regulating growth, differentiation and survival of hematopoietic progenitor cells. The gene for G-CSF is located on chromosome 17 and encodes a protein whose molecular weight varies from 18-22 kd. The primary target of G-CSF is the colony-forming unit-granulocyte (CFU-G), and it exerts its primary effects *in vivo* on late progenitors. In addition to stimulating the differentiation of granulocyte precursors, G-CSF has also been shown to enhance the function of mature effector cells. Human G-CSF has been purified, and the gene cloned. The subsequent expression of the gene in E. coli has made large quantities of purified homogeneous G-CSF available for clinical use. Recombinant G-CSF is a human protein grown in an E. coli vector. Cells expressing G-CSF are grown in culture under sterile conditions. The cells are harvested, and the G-CSF is extracted and purified. Filgrastim is supplied by Amgen as a clear, colorless solution in single-use vials at a concentration of 0.3 mg/ml. Vials contain either 1 ml or 1.6 ml. The drug is generally administered as a subcutaneous injection but may be diluted in 5% dextrose solution for intravenous infusion. It is administered at a dose of 10 mcg/kg/d for 5 days.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

- Age ≥ 60.
- Patients with a new diagnosis of histologically confirmed (according to WHO classification 2008) acute myeloid leukemia (either primary or secondary AML) are included.
- Patients must have a healthy blood-related donor (parent, child, sibling) willing to undergo apheresis after G-CSF administration.
- Karnofsky performance status ≥ 70%.
- Hepatic function - total bilirubin ≤ 2 and, AST ≤ 2.5 **x** upper limit of normal, unless liver is involved with disease or a history of Gilbert's disease.
- Renal function – adequate renal function as demonstrated by a serum creatinine <2 mg/dl.
- LVEF ≥ 50% as determined by echocardiogram or MUGA.
- Ability to give informed consent.

6.1.2 Donor Eligibility

- Donor is blood-related and HLA-haploidentical to the recipient.
- Donor ≥18 years old.
- Donor has undergone serologic testing for transmissible diseases as per blood banking guidelines for organ and tissue donors. Tests include but are not limited to: HepBsAg, HepBsAb, HepBcAb, HepC antibody, HIV, HTLV I and II, VZV, CMV and VDRL, and West Nile Virus . Donor must have normal negative test results for HIV, HTLV I and II, and West Nile Virus.
- Donor has a CXR and EKG performed.
- Donor is not allergic to G-CSF.
- Donor must be able to undergo leukapheresis.
- Donor is not pregnant.
- Donor does not have concurrent malignancy or autoimmune disease.
- Ability to give informed consent.

6.2 Subject Exclusion Criteria

- Patients with a diagnosis of acute promyelocytic leukemia (according to WHO classification 2008).
- Major surgery or irradiation within two weeks.
- Previous therapy with cytotoxic agents for AML. Persons with previous treatments for myelodysplasia/myeloproliferation such as hydroxyurea, interferon, hypomethylating agents (5-azacitidine or decitabine), lenalidomide, or JAK/STAT inhibitors may participate but must have >1 week off therapy prior to enrollment.
- Active CNS disease.

- Uncontrolled infection.
- Pregnant or lactating women – they are excluded, given the potential teratogenic effects of chemotherapy and agents used in the therapy.
- Male and female patients of child-bearing potential unwilling to use effective means of contraception.
- HIV or HTLV I/II seropositivity.
- Concurrent active malignancy other than AML requiring therapy.
- Clinically significant cardiac disease (NY Heart Association Class III or IV) or pulmonary disease.
- Inability or unwillingness to comply with the treatment protocol, follow-up, or research tests

6.2.2 Donor Exclusion

- Donor has cardiac risk factors precluding ability to undergo leukapheresis.
- Donor has evidence of concurrent malignancy or autoimmune disease.
- Donor is pregnant.

7.0 RECRUITMENT PLAN

Patients who fulfill the eligibility criteria as listed in Section 6.0 will be recruited for this study by an Attending Physician of the Leukemia Service. Informed consent will be obtained by one of the participating investigators authorized to obtain consent. A copy of the signed informed consent will be placed in the medical record, as well as in the research file.

This protocol will take due notice of NIH/ADAMHA policies concerning inclusion of women and minorities in clinical research populations. We expect that the study population will be fully representative of the range of elderly patients referred for leukemia without exclusion as to gender, or ethnic background within the limits of being able to identify a suitable PBSC donor. Pregnant women are excluded from participation in this study.

8.0 PRETREATMENT EVALUATION

8.1 Pretreatment evaluation of the patient

The following tests must be performed prior to enrollment. Blood counts, chemistry, and disease assessment must have been performed within 28 days prior to starting chemotherapy regimen or less as clinically indicated:

- Complete history, review of systems, physical exam (including performance status) and informed consent
- Bone marrow biopsy (aspirate and trephine core, if clinically indicated) for morphology with surface markers, for documentation of disease status
- CBC with differential, comprehensive metabolic panel (CMP), LDH, and serum uric acid basic coagulation profile. ABO type and screen
- Urinalysis

- EKG and either echocardiogram or MUGA scan with measurement of left ventricular ejection fraction
- Chest radiograph
- Serum testing for cytomegalovirus (IgG and IgM), toxoplasmosis, herpes zoster, Epstein-Barr virus (EBV)
- Peripheral blood to the Diagnostic Molecular Pathology laboratory for chimerism studies
- HLA genotyping

8.2 Pretreatment evaluation of the donor

Any consenting healthy family donor who is HLA haploidentical with the recipient will be given priority as a potential donor for G-PBSC. The donor (or the donor's parent for minors) must also provide signed informed consent to receive a 5-day course of G-CSF followed by leukapheresis.

In preparation for the stem cell donation, the donor will provide informed consent and then undergo the following evaluation. In general, the following tests must be performed within 7 days of initiating cytoreduction:

- Complete history, review of systems, and physical exam
- Complete blood count and differential
- Comprehensive panel
- Coagulation profile
- Type and Screen
- EKG and chest x-ray (if clinically indicated)
- Serum will be tested for antibodies for CMV (IgG and IgM), HIV-1,2, HTLV1, 2, toxoplasmosis, Hep B, Hepatitis C, Hepatitis B surface antigen, Herpes Simplex, Herpes Zoster, Epstein-Barr virus, VDRL
- West Nile Virus PCR, Hepatitis C PCR and HIV PCR
- Pregnancy test for females of childbearing age
- HLA and KIR genotyping
- Short tandem repeat polymerase chain reaction profiling (for chimerism evaluation)

9.0 TREATMENT/INTERVENTION PLAN

9.1 General: This is a single center trial to assess the feasibility of standard induction chemotherapy followed by a single dose of unmanipulated G-PBSC for the treatment of elderly patients with newly diagnosed AML.

9.2 Pre-treatment: Patients will be treated as inpatients at MSKCC. Supportive care including fluid hydration and prevention of tumor lysis syndrome are provided as clinically indicated by the inpatient Leukemia Service attending.

9.3 Induction Chemotherapy

Induction:

Patients with newly diagnosed AML will receive standard induction chemotherapy with daunorubicin and cytarabine (7+3 scheme) as outlined below:

DAY	1	2	3	4	5	6	7	8	9-11
Cytarabine (100 mg/m^2 IVCI)	X	X	X	X	X	X	X	rest	G-PBSC infusion
Daunorubicin (60 mg/m^2 IVP)	X	X	X						

Consolidation:

Patients who achieve CR may undergo consolidation chemotherapy at the discretion of the treating leukemia physician. If there are remaining cryopreserved G-PBSC after the first infusion these may be infused after one additional consolidation chemotherapy cycle as below. Any further cycles of chemotherapy will be performed without G-PBSC support.

DAY	1	2	3	4	5	6	7-9
Cytarabine 1.5-3 g/m^2/BID	X		X		X		G-PBSC infusion

9.4 G-PBSC Infusion

G-CSF-mobilized peripheral blood cells will be collected from the donors in the Donor Room according to standard MSKCC BMT guidelines. The stem cell product is delivered to the Cell Therapy Laboratory, cell counts will be performed, and the stem cell product processed per institutional guidelines. Up to 84 hours after the completion of chemotherapy, patients will receive an infusion of unmanipulated PBSC.

To reduce the risk of full donor chimerism and GVHD, the PBSC cell dose will be restricted for:

- CD34+ cells (not to exceed 2x10e6/kg)
- CD3+ cells (not to exceed 1x10e8/kg)

Donor treatment: G-CSF administration for PBSC mobilization in donors is outlined below:

DAY	1	2	3	4	5	6	7	8	9
G-CSF (10 µg/kg SQ)				X	X	X	X	X	Pheresis

Donor cell cryopreservation: Donor cells not used in the initial G-PBSC infusion will be stored in the MKSCC Cell Therapy Lab for use after a subsequent consolidation.

9.4 Supportive Treatment: Patients will receive antibiotics, packed red blood cell transfusions, and platelet transfusions according to MSKCC standard care guidelines. Patients with an absolute neutrophil count < 500 cells/μL will receive G-CSF 5 μg/kg/day starting day +1. If there is evidence of ongoing leukemia (circulating blasts, >5% bone marrow blasts) the patient may stop G-CSF at the discretion of the investigator.

9.5 Selection of an immunogenetically optimal donor: Donors will be selected on the basis of KIR/HLA interactions that favor the reduction of relapse whenever possible. In the event that a favorable donor is identified this donor will be selected provided they are eligible. If a favorable donor does not exist an unfavorable donor may be used. Donor favorability is defined as follows:

1. If the patient lacks expression of any KIR ligand (HLA-C1, -C2, or –Bw4) a donor that expresses this ligand ("missing self") is considered favorable.
2. In the absence of missing self pehenomenon, donor selection is based on minimizing inhibitory KIR signaling and maximizing activating KIR siganaling in the following order:
    a. Donors with KIR3DL1 allotypes that generate weak inhibitory signaling
    b. Donor who express KIR2DS1 and HLA-C1
    c. Donors who are homozygous for centromeric haplotype B
3. In the absence of #1 or #2 any available donor may be used for donation. Donors are considered to be eligible based on availability, therefore these selection criteria should not delay treatment if another donor is available to donate on schedule.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

10.1 Post-Treatment evaluation

Treatment evaluations are summarized in the following table. Scheduled evaluations are performed daily during inpatient treatment. Long term follow-up evaluation days may be performed ±7 days to accommodate for patient schedules. Evaluations may be withheld if the treating physician feels that there is a strong contraindication to performing the study (e.g. patient has relapsed and is terminally ill). Also, additional tests will be performed as clinically indicated.

ACTIVITY	START OF THERAPY TO DISCHARGE	DISCHARGE TO DAYS 100
Karnofsky score		+100±7
History and physical	Daily until discharge from hospital	As per out-patient schedule
Chemistry	Daily basic electrolyte panel with biweekly comprehensive metabolic panel	As per out-patient schedule

	(CMP)	
Counts/differential	Daily, with differential when WBC ≥ 0.5	As per out-patient schedule
Disease evaluation, Bone marrow aspirate and chimerism		After hematologic recovery, approximately day 28-40.
Peripheral Blood Chimerism, T-Cell and NK-cell	Day 21 - 25	
GVHD evaluation	Daily after engraftment until discharge from hospital	Weekly for the first month, then biweekly for the following 8 weeks, then as per out-patient schedule

During the first 100 days patients will be closely monitored as per standard of care. Acute GVHD will be assessed and graded according to current MSKCC guidelines. Follow up assessment for disease status by physician should also be completed approximately 1 year (± 2 weeks) post transplant.

10.2 Research Samples

Research blood samples will be obtained from patients at time points indicated (See table) to determine KIR genotyping, NK phenotype (CD94/NKG2A, ILT-2, KIR expression), NK function (intracellular INF-γ, cytotoxicity), and chimerism.

ACTIVITY	PRE-TREATMENT	START OF THERAPY TO DISCHARGE	DISCHARGE TO DAYS 100
Leukemia sample	When available: BM sample (2 EDTA tubes) and PB (3 EDTA tubes)		
Peripheral blood for NK phenotype by flow cytometry (CD94/NKG2A, ILT-2, KIR expression)	At the enrollment of donor and patient (before treatment)	Day +28-35	Day +100±7
Peripheral blood for NK function by intracellular IFN-γ or cytotoxicity	At the enrollment of donor and patient (before treatment)	Day +28-35	Day +100±7

* If donor T-lymphocyte chimerism is >5% a repeat study will be performed at 2 week intervals until chimerism is ≤5%

11.0 TOXICITIES/SIDE EFFECTS

Toxicity Grading: Toxicity will be graded according to the NCI Common Toxicity Criteria, version 4.0.

11.1 Risks to Related Peripheral Blood Stem Cell Donors

The risks of short-term treatment with G-CSF are likely negligible. However, administration of GCSF is frequently associated with low grade fever and low back pain which usually resolves within one day following cessation of GCSF treatment. Furthermore, there has now been one recorded patient who developed acute splenomegaly and splenic rupture in response to high dose GCSF. Bone pain may require treatment with analgesics. The risks of leukapheresis include temporary paresthesia in the perioral, circumoral, and acral areas as well as muscle stiffness and spasm secondary to hypocalcemia, pain and bruising at the needle insertion sites, vasovagal response to venipuncture, and the minimal hemodynamic alterations associated with single unit phlebotomies. To protect against these risks, leukaphereses are conducted in the Blood Bank Donor Room with full medical and nursing supervision and support systems to address adverse events.

11.2 Risks to Patients

11.2.1 Risks related to cytarabine:

Likely, some may be serious:

- Blood clots
- Rash
- Swelling or pain of the rectum
- Diarrhea, loss of appetite, nausea, vomiting
- Soreness in the mouth
- Low blood cell counts that may require transfusion
- Fever

Occasional, some may be serious:

- Infection, especially during periods of low white blood cell counts
- Bruising or bleeding
- Allergic reaction that may cause rash, low blood pressure, wheezing , shortness of breath, or swelling of the face or throat
- Numbness and tingling in the arms and legs
- Kidney damage that may require dialysis
- Headache
- Chest pain
- Hair loss

- Liver damage
- Swelling or irritation to the outside of the eye

Rare but serious:

Injury to the cerebellum, causing difficulty with movement**11.2.2 Risks related to daunorubicin:**

Likely, some may be serious:

- Hair loss
- Nausea, vomiting
- Pink discoloration of urine, sweat, or saliva
- Low blood counts (neutrophils, red-blood cells, platelets)

Occasional, some may be serious:

- Damage to the heart that may lead to fatigue or shortness of breath
- Infections, especially during periods of low white blood cell count
- Anemia that requires transfusion
- Bruising or bleeding
- Dark discoloration of the nails or skin
- Loss of nails
- Redness and pain at a site of previous radiation
- Swelling or redness at the site of injection
- Diarrhea or mouth pain

Rare but serious:

- Other cancers of the bone marrow
- Allergic reactions that may cause rash, low blood pressure, wheezing, shortness of breath, or swelling of the face or throat

11.2.3 Risks related to donor G-PBSC infusion:

Likely:

- None

Less likely:

- Infusion reactions. Patients may experience temporary allergic reactions to the donor cell product including hives, flushing, rapid heart rate, itching, or rash. These may be treated with anti-histamines and/or acetaminophen when appropriate.

Rare but serious:

- Graft *versus* host disease (GVHD). GVHD is a syndrome where donor cells target and attempt to reject normal tissues in the patient. The syndrome may include rash, diarrhea, nausea, vomiting, poor bone marrow function (resulting in low blood cell

counts), and abnormalities in liver function studies. GVHD is treated with steroids to reduce inflammation from donor cells. Rarely GVHD can be fatal.

- Infection. As with any blood product from another human being there is a risk of acquiring a viral or bacterial infection from the cell product. The donors will be tested for infections including hepatitis, HIV, and others according to standard protocol in order to minimize the risk of transmitting any infection.
- Anaphylaxis: Rarely allergic reactions to the donor cell product may cause wheezing, swelling of the face or throat, or low blood pressure.

11.2.4 General risks for patients undergoing chemotherapy:

Infection: Patients with low blood counts may be at risk of bacterial, fungal, and viral infections. Infusion of the donor cell product is not anticipated to increase the patient's risk of infections during the treatment course.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

12.1 Complete Remission (CR) requires that all of the following criteria are met for at least 4 weeks:

Peripheral Blood Counts: The peripheral blood neutrophil count should be ≥1,500/µl (sustained without growth factor support), and the platelets count should be ≥100,000/µl (without transfusion). No circulating blasts (in the absence of growth factor) should be detected.

Bone Marrow Aspirate: The cellularity of the bone marrow should approximate normal. There must be evidence of maturation of all cell lines. The bone marrow aspirate should contain < 5% blasts. Auer rods should not be detected.

Extramedullary Leukemia: Extramedullary leukemia, such as CNS or soft tissue involvement, must not be present.

12.2 CRp (Complete Remission with Incomplete Platelet Recovery) is defined as CR, except that a platelet count is not specified although platelet transfusion-independence must be maintained for at least one week.

12.3 Partial Remission (PR) requires that all criteria for CR be met except that the bone marrow may contain > 5% but < 25% blasts. A value of ≤ 5% blasts in the presence of Auer rods or abnormal morphology is also considered a PR.

12.4 Treatment Failures include patients who do not achieve a CR or PR due to persistent disease or complications of cytopenias.

12.5 Relapse is defined as reappearance of blasts in the blood or the finding of > 5% blasts in the bone marrow not attributable to another cause.

12.6 Treatment-Related Mortality will be defined as death of the patient due to toxicity of the chemotherapy, toxicity from prophylactic measures and treatment procedures for side effects and complications, pancytopenic complications such as infections, and immunological complications such as GVHD.

12.7 Graft versus Host Disease (GVHD)

Acute GVHD is manifested by skin rash, nausea, vomiting, diarrhea and ulceration of the intestines, hyperbilirubinemia and hepatitis, and suppressed or delayed recovery of the hematopoietic and immune system. Standard BMT-CTN and IBMTR systems clinical criteria will be used to establish and grade acute GVHD (See appendix A).[30] In the first 100 days after stem cell infusion patients will be assessed for the development of acute GVHD. Patients with acute GVHD will be treated with immunosuppression as per standard Adult Allogeneic Bone Marrow Transplantation service guidelines.

Chronic GVHD is characterized to varying degrees by sclerosis of lacrimal and salivary ducts, scleroderma-like changes of the skin, chronic inflammation and scarring of the gastrointestinal tract with consequent malabsorption and diarrhea, inflammation of the liver, suppression of the immune system and occasionally other auto-immune phenomena (e.g. auto-immune hemolysis) or involvement of other organs (e.g. pulmonary involvement). Chronic GVHD will be diagnosed and graded according to NIH consensus criteria.[31] Patients will be assessed for chronic GVHD at day 100, 6 months and annually after stem cell infusion, and more frequently if clinically indicated. Chronic GVHD will be treated with standard immunosuppressive therapy as per standard Adult Allogeneic Bone Marrow Transplantation service guidelines.

12.8 Poor Hematopoietic Recovery

Hematopoietic failure is diagnosed when (1) the patient fails to achieve an ANC $\geq$ 500/μl for 3 consecutive days within the first 42 days post-stem cell infusion in a patient who had a sustained ANC ≥ 500/µL prior to therapy or (2) in the absence of relapse, there is absence of patient cells in the blood and/or marrow as demonstrated by chimerism assay. If the clinical criteria for bone marrow failure are fulfilled, infusion of donor stem cells will occur within 2 months of G-PBSC infusion.

12.9 Early Deaths

Early deaths are defined those patients who die within 4 weeks of beginning therapy. Patients who die of treatment associated complications before this timeline will be considered early deaths and inevaluable for leukemia response, but evaluable for toxicity and overall survival (OS).

12.10 Lost to Follow Up

Those patients, in whom there is inadequate information to determine response to therapy or toxicity due to loss of contact with the patient, will be considered lost to follow-up and will be deemed inevaluable.

12.11 Major Protocol Violation

Deviations from the treatment program by either adding a therapeutic agent, or receiving concomitant radio- or other chemotherapy will be considered a major protocol violation. Patients who receive care that is considered to be a major protocol violation will be deemed inevaluable.

13.0 CRITERIA FOR REMOVAL FROM STUDY

If at any time the patient is found to be ineligible for the protocol as designated in the section on Criteria for patient/subject eligibility (e.g. a change in diagnosis), the patient will be removed from the study. Participants may be removed from the study if at any time it is determined to be in the participant's best interest to do so. Also patients may be removed from the study if requested by the patient. Management will depend on where they are in their treatment course. Such patients will receive appropriate supportive care.

14.0 BIOSTATISTICS

This is a pilot study designed to assess the feasibility and an initial study of the efficacy of chemotherapy followed by G-CSF mobilized stem cells from haplo-identical related donors of AML patients above the age of 60. The study will use a two-step enrollment process. First, patients eligible for this study with potential haplo-identical donors will be registered. Second, potential donors are screened by HLA/KIR genotype, and the immunogenetically optimal donor selected. The feasibility objective will examine whether a sufficient percentage of prospective patients that are eligible for this protocol are enrolled and undergo the stem cell infusion. The efficacy objective will provide pilot data for the response rate among patients that receive the stem cell infusion.

To assess feasibility, we will determine the number of patients screened in order to treat 15 patients with the stem cell infusion. For this endpoint, a success indicates that a screened patient undergoes the infusion. A design that differentiates between success rates of 0.10 and 0.20 will be used to determine feasibility. If less than 90 patients are screened in order to attain the 15 patients that are treated with the stem cell infusion, then we will declare this approach feasible. The probability of declaring the screening process feasible is ≤ 0.10 when the success rate in the population is 0.10 and increases to ≥ 0.90 when the success rate in the population is 0.20. The probability calculations are based on the negative binomial distribution.

The study will be terminated in the event of a single observation of a grade III or IV graft versus host disease, a death due to the stem cell infusion, or a recorded aplasia within 42 days of the infusion.

At the conclusion of the study, the following descriptive statistics will be generated:

- The probability of receiving treatment among patients enrolled on the study
- The probability of a complete response
- The median duration of neutropenia and thrombocytopenia
- The median duration of hospital stay

In addition, the cumulative incidence function will be used to generate over time the probability of treatment related mortality, graft versus host disease, grade 3-4 infection, and greater than 5% donor chimerism. Immunologic recovery of NK, T and B cell populations over time will be estimated using nonparametric curve smoothing methods. It is anticipated that the study will be completed within 18 months. If the study requires longer than 18 months for completion, then we will consider a modification to the study design in order to increase the accrual rate.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

15.2 Randomization

There is no randomization.

16.0 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.

The data collected for this study will be entered into the Clinical Research Database (CRDB). Source documentation will be available to support the computerized patient record.

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: *http://mskweb2.mskcc.org/irb/index.htm*

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.0 PROTECTION OF HUMAN SUBJECTS

Risks: From the studies that have been done so far it appears that adding G-PBSC to standard induction chemotherapy can safely be performed in elderly patients with AML and that these patients may benefit from the treatment. However, given this is a new treatment approach, it is possible that there are side effects that have not yet been seen.

Benefits: This protocol may benefit patients by shortening the duration of chemotherapy-induced aplasia, reducing the related severe complications rate (infections, hemorrhagic events etc). This protocol may result in higher anti-leukemic activity compared to standard chemotherapy, achieving higher CR rate and translating in higher OS. The information from this study will help future leukemia patients.

Possible toxicities/side effects: Toxicities and side effects of the agents used are listed in section 11 and reporting of serious adverse events is found in section 17.2.

Consent Process: Participation in this study is voluntary. All patients will be required to sign a statement of informed consent which must conform to MSKCC IRB guidelines.

Alternatives: Alternative treatment options will be presented to the patient prior to taking part in this study. Alternative treatment options may include getting treatment with standard chemotherapy; taking part in another study; or getting no treatment.

Costs/Incentives: No incentives will be offered to patients/subjects for participation in the study. Participation is voluntary. The patient/subject will be responsible for the costs of standard medical care, including the conventional agents cytarabine and filgrastim, antibiotics, blood and platelet transfusions, radiographic studies, laboratory tests, and all hospitalizations, even for complications of treatment. Research tests will be done at no cost to the patient.

Confidentiality: Every effort will be made to maintain patient confidentiality. Research and hospital records are confidential.

17.1 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.2 Serious Adverse Event (SAE) Reporting

Any SAE must be reported to the IRB/PB as soon as possible but no later than 5 calendar days. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org. The report should contain the following information:

Fields populated from CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition

- Indication if the subject remains on the study
- If an amendment will need to be made to the protocol and/or consent form.

The PI's signature and the date it was signed are required on the completed report.

For IND/IDE protocols:
The CRDB AE report should be completed as above and the FDA assigned IND/IDE number written at the top of the report. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office.

All patients will be followed for safety and toxicity related to the study. Potentially serious toxicities are an expected part of this therapy. The reportable serious adverse events (SAEs) will be defined according to current MSKCC BMT Service SAE Guide (Appendix B).

17.2.1

If this protocol is an Industry or Cooperative group protocol, the SAE reporting information should also be included in this section. If the protocol has an IND, this section should include that the SAE will also be reported to the FDA through the IND Office and that the report must include the FDA assigned BB-IDE, BB-IND or IND number and name.

18.0 INFORMED CONSENT PROCEDURES

Patients recruited to this study are elderly individuals with newly diagnosed or relapsed AML who are suitable for intensive chemotherapy.

Prior to consideration for this study, all patients undergo a series of consultations discussing the risks and potential benefits of induction chemotherapy and the different procedures which are a normal part of the leukemia treatment. The risks and potential benefits of the procedure, as well as the participation in a research protocol are also discussed.

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form. Related donors will also sign a consent form, which reviews the risks and alternatives to G-CSF-elicited PBSC mobilization, and collection of PBSC via leukapheresis.

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20.0 APPENDICES

Appendix A: Acute GVHD Grading Scale (IBMTR) [30]

	Skin Involvement			Liver Involvement			Bowel Involvement	
Index*	Stage	Extent of rash		Stage	Total bilirubin (µmol/L)		Stage	Volume of diarrhea (mL/day)
A	1	< 25%		1	< 34		1	< 500
B	2	25-50%		2	34-102		2	500-1500
C	3	>50%		3	103-255		3	>1500
D	4	Bullae	or	4	> 255	or	4	Severe pain or ileus

*Assigned based on maximum involvement in an individual organ system.

Appendix B: MSKCC BMT Service SAE Guide