Phase I Trial Of Autologous Peripheral Blood Stem Cell Reinfusion For Those With Myelodysplastic Syndrome

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A. Objectives

1. To evaluate the toxicity of this chemotherapy regimen.
2. To evaluate the overall survival and disease free survival of patients with MDS treated with high dose chemotherapy followed by stem cell rescue.
3. To evaluate the ability to harvest the required amount of stem cells in those with MDS.
4. To evaluate the presence or absence of cytogenetic abnormalities in those post autologous stem cell reinfusion.
5. To evaluate clonality of peripheral blood stem cells (PBSQ based on x chromosome inactivation by PCR analysis in female patients.

B. Background

Myelodysplastic syndrome (MDS) is a term used to describe the clinical entity in which patients have refractory cytopenias and whose marrows are characterized by morphologic: evidence of dysplastic changes in at least two of the three hematopoietic cell lines and who have a propensity to undergo transformation into acute myeloid leukemia (AML). Patients can be divided into five groups depending on the morphological type of MDS. These include refractory anemia (RA), refractory anemia with ringed sideroblasts (RARS), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMML). These subgroups are associated with the percentage of blasts in the bone marrow. RA and RARS have less than 5% blasts, RAEB has 5-20% bone marrow blasts, RAEB-T has 21-30% blasts and AML has greater than 30% blasts. The clinical course of these patients with MDS varies widely, from an indolent course with relatively few complications to a rapid evolution to AML. The AML that develops from MDS is generally more resistant to standard induction therapy and the life expectancy is poor

MDS usually presents as refractory cytopenia, usually in the elderly with greater than 80% of the patients being over 60 years old. The incidence of MDS is about 220-450 per million in the population over 70 years of age.

Supportive care is the mainstay of therapy for those with an indolent form of MDS. For those at risk of AML transformation, therapy is often times limited by concomitant medical problems in this usually elderly population. Given such a poor prognosis for those a high risk of AML transformation, patients in better general medical health have undergone intensive chemotherapy with variable complete remission rates from 13 to 41%. This comes at unacceptably high rates of therapy related morbidity and mortality. Moreover, these complete remissions are generally short lived. Allogeneic bone marrow transplants have also been used to treat MDS and offers the sole possibility for cure and prolonged survival. This option is only available, however, to a minority of patients, and the survival benefits only outweigh the toxicities involved in those who are quite young (29-39 years of age). Low dose chemotherapy has been evaluated as well, but in all studies there has been no survival benefit.

a. Staging

Those who would benefit the most from this therapy are those a greatest risk for morbidity and mortality from MDS. As mentioned above, there are five morphological subgroups of MDS. Each subgroup has a different prognosis. From a meta-analysis done by Hoffman and Boswell, those with RAEB-T had a medial survival of 5 months, with a 50% chance of AML transformation. In contrast, the

least aggressive MDS subgroup is RARS with a median survival of over 6 years. The statistics for all groups is listed in table **1.**

	MDS Subgroups			
	RA	RARS	RAEB	RAEB-T
Median Survival (months)	43	73	12	5
Trnasformation to AML (%)	15	5	40	50

Other prognostic indicators are the cytogenetics of the bone marrow cells. Those with complex chromosome abnormalities or single chromosome abnormality involving -7 or 7q- or +8 have median survivals ranging form 3 months in the former group to approximately 20 months in the latter. Conversely, those without a chromosomal abnormality have much longer median survival, greater than 3.5 years. Again, see the table below.

Chromosomal Abnormality					
	Complex Defects	Monosomy 7 or deletion 7q	Trisomy 8	Deletion 5q	Normal Chromosomes
Median Survival (months)	3	11	18	47	>50

b. Conventional therapy

One therapeutic approach is to divide patients into groups according to their age and risks of developing AML. Patients over physiologic age 70 generally would not tolerate allogeneic bone marrow transplant or high dose chemotherapy and therefore supportive care with or without low dose chemotherapy and colony stimulating factors are acceptable treatment options. For younger patients (less than 70) in otherwise excellent clinical condition, an allogeneic bone marrow transplant in the best option for those at high risk of AML transformation. For those patients without a matched donor, an autologous transplant or high dose chemotherapy are the only options.

c. Chemotherapy

Low dose chemotherapy using arabinoside has resulted in a 10-20% complete response rate. These responses were short lived, and a randomized trial evaluating arabinoside against supportive care only showed no survival benefit. Additionally, those receiving arabinoside had significant toxicities.

More intensive chemotherapy regimens have reported slightly better complete response rates, from 13-51%. This comes at significant risk of chemotherapy related severe morbidity and mortality. Again, the durations of remissions are usually short. Agents used have included high dose arabinoside and rubidazone.

d. Allogeneic Bone Marrow Transplantation

The use of allogeneic bone marrow transplant (BMT) is the only chance of cure and long term survival for many patients with MDS. A review of the literature on this topics yields varying disease free survival (DFS) probabilities. The most recent report by Mattijssen, et al., enrolled 35 patients with a median age of 41. They were given cyclophosphamide and total body irradiation (TBI) with or without idarubucin. The DFS at 2 years was 39%, this number rising for those who were transplanted for RA to 73%. There were 14 transplant related deaths, however.

Another study by Anderson, Appelbaum, et al., followed 31 patients with a more advanced morphology of myelodysplasia (RAEB, RAEB-T, or CMML) after cyclophosphamide, busulfan, and TBI followed by BMT. DFS at 3 years was 23%. This group had lower relapse rates than a previous study without busulfan (28% as compared to 54%), but had much higher nonrelapse mortality (68% versus 36%).

The same group reported results on 93 patients post BMT using cyclophosphamide and either busulfan or TBI. All patients had greater than 5% blasts, and 63 had HLA identical siblings. The DFS for these patients was 41% at 4 years, rising to 62% DFS for those under 40.

e. Autologous Bone Marrow Transplantation

There have been very few studies on autologous bone marrow transplantation for those with MDS, all of which have been small, non-randomized pilot studies. The one published study by Laporte, et al, followed seven patients with a relatively young median age (44). They all had refractory AML transformation, but with different myelodysplastic syndromes; three with RAEB, one with RAEB-T, another with CMML, and the last two did not have an MDS diagnosis prior to AML transformation. Four patients relapsed at 2.5, 6, 8, and 25 months post transplant and two maintained a DFS at 10 and 28 months. One died of transplant related toxicity. This study was promising and showed the prospect for a cure ' butthe study was very small. Furthermore, the study used bone marrow collection, as opposed to stem cell collection, for re-engraftment and had one death due to sepsis during neutropenia. The proposed study differs by using peripheral blood stem cell reinfusion (PBSCR) and therefore expects to limit transplant related toxicity by providing a shorter duration of re-engraftment and therefore a shorter course of pancytopenia.

Two studies evaluating autologous stem cell reinfusion were published as abstracts in the journal Bone Marrow Transplant., One study by Carella, AM, et al, showed that a successful harvest of stem cell progenitors was possible in those with RAEBT and AML transformation. They studied 9 patients. All of the patients received idarubicin, arabinosylcytosine, and etoposide for mobilization of their stem cells, as well as G-CSF. All 9 tolerated the mobilization, and in 7 of the 9 patients they were able to obtain an adequate number of CD34+ cells for re-engraftment. Three of these patients underwent autografting, with one patient in complete remission after 6 months, one patient relapsing in two months who died of refractory leukemia, and the third discharged at the time of publishing in remission. This study is also promising, in that 9 of 9 patients were able to tolerate mobilization and 7 of 9 able to successfully produce adequate numbers of stem cells (CD34+).

A final study published as an abstract by Demuynck, H, et al., investigated the feasibility of PBSCR. 4 patients with RAEB-T underwent mobilization and 3 generated adequate stem cells during leukophoreses (>1 106 CD34+ cells). Cytogenetics showed a normal karyotype in all stem cells. All three underwent reinfusion after busulfan/cyclophosphamide therapy. Follow up on this study was too limited to report any survival data.

C. Rational for Study

There remain a substantial number of patients with CP-CML without matched related or unrelated donors or who refuse MUDT. The absence of cure with standard therapy and the encouraging results of unmanipulated PBSCR makes this a viable alternative that warrants, further evaluation.

We propose IC chemotherapy, both as a means of in vivo purging to mobilize a higher proportion of karyotypically normal PBSC's for harvesting and also for reduction of tumor burden. The latter may positively influence complete response attainment and survival. Harvested cells will be examined for normal karyotyping by PCR. Clonality studies based on X-chromosome inactivation by PCR analysis will be performed on all female patients.

Post PBSC harvesting therapy will be at the discretion of the referring physician. Patients will be admitted to PBSCR if criteria for autologous BMT as defined in section 10.1 are fulfilled.

A graft versus host (GVH) like syndrome can be induced in autologous BMT by cyclosporin A (CsA) administration. This results in the production of MHC class II autoreactive cytolytic effector cells,

with enhanced anti tumor effect. In the animal model, adjuvant IFN gamma appears to upregulate class II antigens and enhance this effect. In patients with metastatic breast cancer, Kennedy et al have demonstrated that CsA induced GVHD can be augmented by IFN gamma without increased toxicity or delay in haematopoetic recovery. The syndrome was self limiting with a 36% incidence of grade III skin rash treatable with topical steroids. The existence and extent of any anti-tumor effect in this context of breast cancer remains to be determined.

The GVH effect is probably significant in those undergoing BMT for RAEB or RAEB-T. Evidence for this is based both on increased survival in other leukemias with evidence of graft versus host disease post allogeneic BMT and the few studies which have looked at allogeneic BMT for high risk MDS. Post PBSCR, patients will receive immunotherapy with IFN gamma and cyclosporin A in an attempt to induce GVH like disease. A recently approved cytoprotective agent, amifostine, has been shown to afford protection of normal marrow progenitor cells while sensitizing leukemic stem cells to the cytotoxic effects of alkylating agents and organoplatinums. Amifostine has also been shown to provide a hematopoietic improvement in those with MDS, in both an increase in platelet counts and a 50% reduction in the number of transfusions required. We therefore propose amifostine treatment prior to cyclophosphamide therapy in efforts to both increase the death of MDS cell progenitors and to salvage normal stem cells, thereby decreasing the length of pancytopenia post high dose chemotherapy and PBSCR.

D. Eligibility

- The diagnosis of MDS with RAEB, RAEB-T, or CMML according to FAB criteria, or the presence of MDS with abnormal cytogenetics, specifically complex defects, monosomy 7, or trisomy 8.
- The diagnosis of MDS of any subgroup but with AML transformation.
- Age 18 to physiologic 70 years
- The absence of a suitable sibling allogeneic donor.
- Patient refuses unrelated donor transplant or none available
- Clinical parameters

Clinical Parameter	Value
Left ventricular ejection fraction	≥50%
DLCO	≥60% of predicted
Performance status	0-1 (ECOG)
Bilirubin	< 2x normal
SGOT	< 1.5x normal
Creatinine	< 1.5 x normal
WBC	≥ 3,000/~tl
Platelets	≥ 100'000/µl
HIV.	negative
Marrow biopsies	myelofibrosis < 3+

E. Patient Entry

- Evaluation by a CU BMT unit attending: who will coordinate (a) appropriate workup to define patient eligibility; (b) marrow harvest operating room time; (c) insertion of indwelling catheter; (d) chemotherapy and PBSC harvest and; (e) high dose conditioning chemotherapy and PBSC re-infusion.

- Consent: Eligible patients who wish to participate must sign informed consent.

- Registration: To register the patient, fax or deliver the completed Eligibility Criteria Form and signed Informed Consent to the Columbia Cancer Center Protocol Office (C3PO), located on PH 8W. Phone (212) 305-8602, fax (212) 305 3035. Send hard copy for faxed registration by intrahospital mail.

F. Required forms

Eligibility Criteria Form
Informed Consent
On Study Form
Summary & Evaluation Form
Summary Update Form

G. Treatment Plan

- Autologous PBSC Harvest
  - Conventional chemotherapy will be discontinued.
  - Unmanipulated bone marrow of PBSC for backup will be harvested and cryopreserved according to standard CU BMT protocol. All patients will have appropriate indwelling catheters inserted.
  - Intensive IC chemotherapy. Patients will receive Idarubicin 6mg/M2/day on day 1-3, and Cytarabine 600 Mg/M2/day on day 1-3. Recombinant G-CSF is commenced 24 hours after chemotherapy at 5 ~Lg/kg until ANC is > 1 x 109/1 for 3 for 3 consecutive days post harvest. See table below.

Drug	*Total Dose (MgIM21day)*	*Day*		
		1	2	3
Idarubicin	6	x	x	x
Cytarabine	600	x	x	x

PBSC will be harvested starting when the WBC is > 1 x 109/1 using CU BMT standard harvesting techniques.

  - Autologous PBSC transplant. Patients fulfilling the criteria will undergo PBSC transplant with previously collected and cryopreserved in vivo purged PBSC
  - Pre-transplant therapy: (a) Allopurinol 200 Mg/M2/day beginning 48 hours before busulfan and discontinued 24 hours prior to PBSC infusion. (b) Phenytoin to achieve therapeutic levels prior to first dose of busulfan. Discontinued at completion of busulfan infusion.
  - Preparative regimen. Busulfan given orally at 1 mg./kg/dose every 6 hours for four consecutive days beginning at 0600 on day -8 and ending at 2400 on day -5 (total dose 16 mg/kg). Patient to remain NPO 1 hour prior and post therapy. Dose repeated if patient vomits within one hour of dose administration.
  - Cyclophosphamide 60 mg/kg infused over 2 hours for two consecutive days, i.e. day -4 and -3 (total dose 120 mg/kg). Mesna, a uroprotectant, is given as a continuous intravenous infusion at a dose of 100 mg/kg for *3* days concurrently with, and after the cyclophosphamide infusion
  - (day -4 to -2).

- Amifostine 910 Mg/M2 as a intravenous infusion over 15 min., with the infusion starting 30 minutes prior to each cyclophosphamide dose (day -4 and day -3).

See table for dosing regimen.

Drug	Dose/day	Day								
		-8	-7	-6	-5	-4	-3	-2	-1	0
Busulfan	*4* mg/kg	x	x	x	x					
Cyclophosphamide	60 mg/kg					x	x			
Mesna	100 mg/kg					x	x	x		
Amifostine	910 mg/m^2									
PBSC										x

- Do not use barbiturates, acetaminophen, or steroids during chemotherapy.
- PBSC reinfusion on day 0

- Immunotherapy Treatment with cyclosporin A (CsA) will commence on the day of PBSC infusion and continue until day *28.* CsA will be infused at *2.5* mg/kg/day as an IN. infusion over *4* hours in *2* divided doses. The dose will be modified by *25%* for serum creatinine *2.2* mg/dI, *75%* for serum creatinine *>3* mg/dI and stopped if serum creatinine *>4* mg/dl. IFN gamma will start on day *7* at *0.025* Mg/M2 s.c. every other day until day *28* following PBSC infusion. Both CsA and IFN gamma will be stopped if the patient develops a stage *3* rash over > 50% of the body and biopsy > 2 GVHD. Skin rash will be treated with topical corticosteroid or systemic steroids if necessary. See table below.

Drug	Dose	Day post PBSCR				
		0	7	14	21	28
Cyclosporin A	*2.5* mg/kg/day	← 4 hour infusion daily →				
IFN gamma	0.025 mg/m^2		← SQ injection QOD →			

- Toxicity

  Toxicity of IC and BuCy:
  - *Hematologic:* Absolute granulocytopenia is expected between day 0 and day 10 and PMN <500/µl until day *14-28.* Life threatening and fatal infections or bleeding may occur.
  - *Hepatic dysfunction:* Transient elevations of AST, ALT, and bilirubin are expected. Hepatic venoocclusive disease which can occur in the setting of high dose Bu Cy chemotherapy is managed supportively but has a mortality of approximately 50% if it occurs.
  - *Gastrointestinal toxicity:* Nausea and vomiting will be treated with antiemetics. Barbiturates and steroids are avoided. Mucositis, dysphagia, and diarrhea are treated with supportive measures.
  - *Cardiomyopathy:* Cyclophosphamide may occasionally produce severe hemorrhagic cardiac necrosis when administered at doses between 120-240 mg/kg. This complication has been observed with doses administered over 1 to 4 days. Idarubicin can produce arrhythmias and cumulative dose cardiomyopathy.
  - *Pulmonary toxicity:* Cyclophosphamide (CPA) induced pulmonary toxicity has been reported. However, each patient had received other drugs in addition to CPA. In half of

the reported cases, clinical recovery from the pulmonary toxicity occurred in 1-8 weeks. Pulmonary fibrosis has been reported with high dose busulfan.

- *Neurological:* At high doses cytarabine can potentially cause cerebellar ataxia and other neuropathies.
- *Genitourinary:* CPA-related gross or microscopic hematuria correlates with the concentration of drug metabolites in the bladder. Should severe hemorrhagic cystitis occur, CPA will be discontinued until hematuria has completely cleared. Mesna has been added to the regimen to limit this toxicity. Renal function will be carefully monitored during therapy and recovery to avoid significant nephrotoxicity. Furthermore, and syndrome of inappropriate ADH secretion has occurred within 24-72 hours follow CPA. Careful clinical management of fluid and electrolytes is usually adequate to control this self-limited syndrome.
- *Dermatological:* Skin ulceration and phlebitis should not occur secondary to drug delivery via a central catheter. A rash is a common complication of high dose cyclophosphamide and can occur with cytarabine and antibiotics. Alopecia is expected. Hyperpigmentation is common with busulfan.
- *Other:* Sterility and/or interruption of menses is expected.

- Toxicity of G-CSF
  - The side effects of G-CSF, if any, are usually mild and brief, and include discomfort with pain, swelling and redness at the site of injection, bone pain, muscle cramps and pain in the back of the legs, phlebitis, arthritis, and psoriasis. Thrombocytopenia or reversible hepatitis may develop.
- Toxicity of Cyclosporin A
  - The side effects are for doses given to prevent organ rejection and may be less common and severe with the present regimen. Tremor, headache, and renal dysfunction are the most frequent side effects. Leukopenia, thrombocytopenia, and anemia may occur. Uncommon gastrointestinal side effects include diarrhea and transient transaminitis.
- Toxicity of IFN gamma
  - Constitutional symptoms of fever, chills, myalgia, and headache are common. Hematological side effects include granulocytopenia, anemia, and thrombocytopenia. Diarrhea, nausea, and vomiting may occur.

- Toxicity of Amifostine
  - The most common side effects are nausea and vomiting, somnolence, sneezing, and a transient, asymptomatic hypotension. Less commonly seen are metallic taste, a Rushed feeling, fever and rash, malaise, hiccups, and chills. Rarely, hypocalcemia occurs and tetany was reported in one patient.
- Drug Formulation, Availability, and Preparation

Tests and Observations	On Study	Prior to Marrow, PBSC harvest	Post PBSC harvest	Prior to PBSCR	Inpatient	Post ABMT follow-up*
History	x	x	x	x	x	x
Examination	x	x	x	x	daily	x
Vital signs	x	x	x	x	daily	x
Weight	x	x	x	x	daily	x
Performance Status	x		x	x	weekly	x
Dental exam	x				prn	

Toxicity Evaluation				x	x	x
CBC with diff, Coags, retics, fibrinogen	x	x	x	x	daily	x
LFT's	x	x	x	x	BIW	prn
Electrolytes	x	x	x	x	daily	prn
HIV, CMV, HSV, VZV, Toxo, Hep.	x	x				
EKG	x					prn
MUGA	x	prn				prn
PFT's	x	prn				prn
UA/micro	x					prn
Bone marrow	x	x	x	x		x
Cytogenetics	x	x	x	x		x
Skin biopsy	x				prn	
CXR	x			x	prn	prn

*post ABMT evaluations are a 3 month interval x one year, the q year x five years.
prn - as clinically indicated.

H. Definition of Terms

a. Removal of Patients from Protocol Therapy

i. Patients will be removed with documented AML transformation at anytime from protocol therapy and be treated appropriately

ii. Extraordinary Medical Circumstances. If, at any time, the constraints of this protocol are detrimental to the patient's health, the patient will be removed from the protocol. In this event, the reasons for withdrawal will be documented and the patient will be followed for survival.

iii. Unexpected or Life Threatening Complications. If this should occur, all direct questions regarding therapy will be directed to the principal investigators. The principal investigators and protocol office will be notified immediately **in the event of an unusual, life threatening, or lethal toxicity.**

I. Ancillary Therapy

Patients will receive full supportive care, including transfusions of irradiated blood and platelet products, antibiotic, antlemetics, etc., when appropriate. Patients who fail to re-establish marrow function will receive backup marrow. The reasons for treatment, dosage, an the dates of treatment should be documented. All blood products administered will be irradiated with 3000 cGy to avoid graft versus host disease. Reverse isolation procedures will be maintained during aplasia until granulocytes are >200~t/l. Patients may participate in supportive therapy trials. Patients with HSV antibodies will be given acyclovir (400 ing PO TID or 5 mg/kg/day IV q8h) until PMN are > 400/μ/ x 2.

Hormones or other chemotherapeutic agents may not be administered except for steroids given with amphotericin B therapy, for treatment of GVH rash, for adrenal failure, or septic shock or hormones

administered for non- disease -related conditions (e.g. insulin for diabetes). Steroids may not be used as antlemetics during high dose chemotherapy administration.

J. Statistical Considerations

The feasibility of PBSC harvest will be evaluated. As well, the effectiveness and toxicity of high dose chemotherapy with autologous PBSCR and immunotherapy will be evaluated.

Accrual: Based on previous experience, the accrual rate of subjects is expected to be approximately 5 per year. Thus, 20 evaluable subjects will be accrued over 4 years. These patients will be followed until death. The primary analysis of these patients will take place after 1 year of follow up.

Analysis Plan and Power Calculations: The proposed treatment is expected to increase the disease free survival (DFS) and overall survival (OS) which are the primary endpoints. the Kaplan-Meier estimator will be computed to assess DFS and OS for this treatment plan.

Conventional chemotherapy of high risk patients yields a one year OS of 5-20% depending on the population studied. DFS is much lower, at one year the expected DFS is 0-5%. The proposed treatment modality will not be of further interest if the one year OS is less than 10%. We expect a OS of 40% and a DFS of about 20-30%, based on autologous BMT pilot studies.

We will use the optimal two-stage stopping rule of Simon8. Under this design, we will do an interim analysis after 7 patients have been enrolled and followed for one year. If fewer than 2 survive for one year, we will terminate the study. If greater than 2 survive for one year, we will continue accrual until 15 patients have been followed for at least one year.

If 4 or fewer survived at least one year, we will reject the new regimen as ineffective. If 5 or more survive at least one year, we will recommend continued use of our regimen. With this stopping rule, the chance of correctly rejecting the new regimen is more than 95% if the true one year OS is 20% or less, and the chance of correctly accepting the regimen is more than 80% if the true one year OS is 40% or greater. Of all two-stage stopping rules with these error probabilities, this particular rule has the smallest expected sample size. Note that with this design, we may stop the trial as soon as 5 patients have survived for one year, even if the target accrual has not been reached.

K. Use Of Facilities

This clinical study will employ inpatient and outpatient facilities at CPMC as well as the clinical laboratories.

L. Method of Patient Accrual

Patients will be referred to the transplant service for initial evaluation by their primary physician or oncologist. A CU BMT unit attending will explain the protocol in detail to the patients and obtain informed consent. All patients treated on this protocol will receive chemotherapy with PBSC harvesting.

M. Risks

The risks are those associated with the chemotherapy discussed in section 7.0.

N. Benefits

Individual patients may benefit from prolonged survival with the potential for possible cure. Society will benefit if an effective therapy is identified for an illness that, except in a minority of allogeneic BMT patients, is still incurable.

O. Alternative Therapies

Alternative therapies include supportive care only, conventional therapy, or other investigational treatments.

P. Compensation

There is no compensation for participation in this study.

Q. Enrollment of Pediatric Patients

No patients under 18 will be enrolled.

R. References

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