Protocol Number: **RP 98-15**

Protocol Title: **ALLOGENEIC BLOOD OR MARROW TRANSPLANTATION FOR HEMATOLOGIC MALIGNANCY AND APLASTIC ANEMIA**

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Confidentiality Statement

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Protocol Summary

Patient Eligibility

1. Diagnosis of aplastic anemia or histologically documented hematologic malignancy

2. The new World Health Organization (WHO) criteria will be gradually adopted for use in classification of hematologic malignancies.

3. Disease Status

Aplastic Anemia

severe disease indicated by marrow cellularity: <25% (or 25-50% cellularity with <30% of remaining cells hematopoietic in origin), or
abnormal peripheral blood counts (2 of 3 values): reticulocytes <1% (corrected for hematocrit), platelets <20 x 10^9/L, neutrophils <0.5 x 10^9/L.

Acute Leukemia

resistant or recurrent disease after combination chemotherapy with at least one standard regimen
first remission patients at high risk of relapse
AML - antecedent myelodysplastic syndrome, secondary AML, high risk cytogenetic abnormalities
ALL - high risk cytogenetic abnormalities
patients in first remission without adverse prognostic factors may be transplanted after discussion and agreement of the transplant team.

Chronic Myeloid Leukemia (CML)

Chronic or accelerated
Patients in blast phase should be treated with TK (Tyrosine Kinase Inhibitors) as first line therapy and/or one standard chemotherapy regimen

Myeloproliferative and Myelodysplastic Syndromes: Myelofibrosis, Refractory Anemia, Refractory Anemia with Excess Blasts, Refractory Anemia with Excess Blasts in Transformation, Chronic Myelomonocytic Leukemia. Patients with P. Vera or Essential Thrombocytosis will be eligible for transplant only if they are in transformation to AML or MDS.

Lymphoproliferative diseases:

Waldenstrom's Macroglobulinemia, low-grade Non Hodgkin Lymphoma - recurrent or persistent, symptomatic disease after first-line chemotherapy.

CLL patients with ≤20% marrow involvement pretransplant will be treated on appropriate non-myeloablative transplant protocols. CLL patients with ≥20% marrow involvement pretransplant will be eligible for this protocol and receive full-ablative therapy.

Multiple Myeloma patients will be treated on appropriate non-myeloablative transplant protocols.

Non-Hodgkin Lymphoma: intermediate and high grade
resistant or recurrent disease after combination chemotherapy with one standard regimen
first remission lymphoblastic or small, non-cleaved cell lymphoma at high risk of relapse
CNS disease, or BM disease and LDH >300

4. Histocompatible donor identified. For unrelated donors, the compatibility criteria of the National Marrow Donor Program must be satisfied. If a compatible cord blood (CB) donor is identified and there is no suitable unrelated donor, the patient may receive a CB transplant (CBT) . For CBT patients, that acute leukemia patients should be in remission.

5. Autologous marrow transplant not possible (or not desirable)
history of marrow tumor (a relative contraindication to autologous transplantation)
inadequate marrow dose
abnormal marrow histology or function prior to storage
thrombocytopenia, leukopenia
marrow cellularity <20%

6. Zubrod performance status 0-2 (Karnofsky ≥ 70%)
For myeloablative regimens

- No KPS requirement for failure to engraft transplants and Reduced Intensity Conditioning with FluMel

7. Age ≥ 4, ≤ 70 years.

8. No serious concomitant medical or psychiatric illness

9. Not pregnant

10. Informed consent

Required Laboratory Data (see section 3.0 for full eligibility criteria)

1. DLCO ≥50% predicted, corrected for HgB or DLVA alveolar ventilation
2. Cardiac ventricular ejection fraction (MUGA scan or echocardiogram) ≥ 50%
3. Bili, Alk phos, SGOT < 3 x normal, unless due to disease
4. Creatinine clearance (CrCl) is ≥ 50 ml/min by 24 hour urine collection or by CrCl calculation
5. HIV screening negative, according to current RPCI Blood Bank Criteria
6. CMV and hepatitis status known
7. If evidence of active viral infection, infectious disease clearance is required

Study Outline

1. Registration: Contact the BMT Coordinator at extension 8963, 3868, 8927, 4192, or 8205 to register patient.

2. Preliminary cytoreductive chemotherapy, if indicated

3. Involved-field radiation, if indicated

4. Transplant Regimens: (Abbreviations: C or Cy – Cyclophosphamide; T or TBI - Total Body Irradiation; Bu – Busulfan; M – Melphalan; Flu – Fludarabine; V or VP-16 - Etoposide; ATG – Antithymocyte Globulin) (See section 5 for details)
   a. CATG
   b. FluM
   c. FluATG

1. INTRODUCTION

1.1. Since its introduction into clinical practice in 1968, bone marrow transplantation (BMT) has become the treatment of choice for severe aplastic anemia (SAA) and chronic myelocytic leukemia (CML), and it plays an important role in the management of other hematologic malignancies offering the possibility of long-term remission or cure for patients who have failed first-line therapy and are unlikely to be cured by other means [(1)]. For all indications, more than 48,000 transplants have been reported to the International Bone Marrow Transplant Registry through 6/1/96. [(2)]

1.2. SAA is fatal in 80% of cases treated with supportive measures alone [(3)]. Immunosuppressive therapy with antithymocyte globulin leads to complete recovery in approximately 20% of patients and partial recovery (without the need for further transfusions) in a similar number; overall 5-yr. survival is 60% [(4)]. Survival after allogeneic BMT is age dependent [(5-7)]:

Age (yrs)	Survival
< 20	75%
20-30	60%
>30	40%

The chief complication of BMT for SAA is graft vs. host disease (GvHD) which is fatal (or leads to fatal infection) in approximately 20% of patients. Other problems are graft rejection (which can occur in up to 20% of cases), infection (without GvHD), and hemorrhage. The best results reported for BMT indicate a 10-yr. survival of 82% in a group of untransfused patients (age 3-32 years) [(5)]. The improvement in outcome for untransfused patients is largely due to reduced risk of marrow graft rejection. For patients with prior transfusions similar results may be achieved by the addition of total lymphoid irradiation (TLI) or total body irradiation (TBI) to the usual high-dose cyclophosphamide regimen [(7,8)]. With these approaches rejection has become less frequent in the group of patients who have had multiple transfusions and survival has improved to 60-70%. Although the addition of radiation may reduce the incidence of the rejection, there are other associated risks. Irradiation may cause late cancers [(8a,8b)] as well as problems with growth, development and fertility [(8c)]. Recently published data suggest that Cyclophosphamide combined with antithymocyte globulin (ATG) may be a more effective regimen than Cyclophosphamide alone in patients who have received multiple transfusions without the attendant risks associated with irradiation. In a report from the Seattle group,

39 patients who received the combination of Cyclophosphamide and ATG had a 3 year survival of 92% vs. 72% in historically treated patients who received Cyclophosphamide alone [8d]. The incidence of chronic graft versus host disease of 32% and the low incidence of graft failure (7%) are similar to values seen in patients who are untransfused.

This is a rare disease and we are unlikely to see more than 2 transplant candidates per year. However, the International Bone Marrow Transplant Registry sponsors a study which examines the use of cyclophosphamide alone versus cyclophosphamide plus anti-thymocyte globulin for conditioning before allogeneic fully HLA matched transplant. Either regimen has been associated with long-term survival approaching 80%. Accordingly, we will participate in this study. If the study is not open or the patient is ineligible for randomization, we plan to deliver the best available BMT care for these patients using a standardized approach, without a research question. Cyclophosphamide/ATG will be given as standard conditioning for all patients with aplastic anemia. Consecutive patients will be reported to the International Bone Marrow Transplant Registry, and outcome also will be compared to published results from other centers. In addition, these patients may participate in ancillary studies which go across diagnoses and are designed to reduce transplant-related complications (e.g., GvHD, CMV infection, etc.). Patients with aplastic anemia in need of an unrelated transplant will be treated as a standard AML patient. This is due to the need for a more aggressive conditioning regimen to prevent graft rejection.

1.3. CML has been considered a universally fatal disease with a median survival of 4 years from diagnosis. Gleevec® (Imatinib) has changed the standard treatment of CML [9a]. Currently, it is not clear when allogeneic transplant should be performed for CML patients. Currently Oregon Health Sciences Center has reported that patients who do not respond to Gleevec within 6 months with a major cytogenetic response will not at further time points after treatment (Richard Maziarz, Brian Druker Personal Communication [9b]). Thus, these patients should be considered for allogeneic transplant. In addition, patients under the age of 30 can be considered candidates for allogeneic BMT because of a lower mortality than older CML patients. Allogeneic BMT, performed during the chronic phase of the disease, results in 60% disease-free survival (DFS) beyond 5 years [9]. Preliminary results indicate that if BMT is performed within the first year of diagnosis DFS is further improved to approximately 80%. Conversely, if BMT is delayed until accelerated or blast phase, DFS is reduced to 15-25% due to resistant leukemia. Patients should be considered for BMT within one year of diagnosis since evolution to blast phase is unpredictable (approximately 25%/year after the first year) and markedly increases the probability of relapse after transplantation.

1.4. Extensive experience with BMT for recurrent acute leukemia and lymphoma indicates that 50-60% of patients can be expected to achieve a complete remission, and half of these will remain free of disease more than 5 years after marrow transplantation (and are probably cured) [10-12]. In comparison, fewer than 10% of these patients can be cured with conventional therapy. The results of allogeneic BMT for acute leukemia and lymphoma in first remission are more difficult to interpret. Disease-free survival of 50-60% is typically reported, and although this is superior to the results of chemotherapy, it may not be superior to chemotherapy followed by BMT for those patients who relapse [10, 11, 13, 14].

1.5. The problems associated with BMT fall into two broad categories, treatment-related toxicity and resistant disease.

1.5.1. Treatment-related mortality is typically 20-25%, and includes regimen-related toxicities (especially infections, interstitial pneumonitis, and hepatic veno-occlusive disease) and complications of graft vs. host disease (GvHD). Patient age and donor histocompatibility are the most important determinants of GvHD mortality which ranges from < 10% for patients

under the age of 20 with an HLA-genotypically identical donor, to >30% for patients over the age of 40, or with partially matched donors [15, 16]. Post-transplant immunosuppression with cyclosporine, usually combined with methotrexate or methylprednisolone, reduces the incidence and severity of GvHD [6]. Removal of T-lymphocytes from the donor marrow is one of the most effective ways to prevent GvHD, but depletion of more than 99% of T-cells (2 logs) increases the risk of graft rejection [17,18]. A variety of methods for T-cell depletion has been employed; the most popular has been the use of antibodies to T-lineage surface antigens, however separation in centrifugal fields (elutriation) and in vitro exposure of marrow to cytotoxic drugs (e.g., methylprednisolone, etoposide) also has been used. Factors that increase the risk of regimen-related organ toxicity are incompletely defined but include extent of prior therapy, performance status at the time of BMT, presence of organ dysfunction prior to BMT, and intensity of the transplant regimen. Cytomegalovirus infection is an important complication, which was responsible for a 10-20% mortality rate after allogeneic BMT. Several recent developments have reduced the risk of fatal CMV infection, including the use of seronegative blood products (and marrow donors when possible) for CMV-negative patients, administration of prophylactic acyclovir and intravenous immunoglobulin (IVIG), treatment of CMV infections with gancyclovir plus IVIG, and the use of blood products that have been filtered.

1.5.2. The frequency of failure due to resistant malignancy depends both on the diagnosis and the timing of the transplant. For example, the relapse rate is approximately 70% after BMT for refractory acute leukemia or CML in blast crisis, compared to 20% for patients with acute leukemia in first remission or CML in the chronic phase [2]. Another factor influencing relapse rate is GvHD; patients who survive despite significant acute GvHD (grade 2 or greater) or chronic GvHD have a reduced risk of leukemic relapse [19]. Of particular importance is the finding of a strikingly high relapse rate for patients with chronic phase CML who received T-depleted marrow. Autologous BMT would be expected to be inferior to allogeneic BMT due to lack of graft vs. tumor effect as well as possible reinfusion of tumor cells (hidden) in the transplanted marrow. On the positive side, autologous BMT avoids the complications of GvHD and marrow rejection.

1.6. It is often difficult to determine the optimum timing for BMT. Balancing anticipated toxicity against tumor response requires consideration of multiple factors, including diagnosis, response to previous (conventional) therapy, age, and donor compatibility. In general, allogeneic BMT is the preferred treatment for any patient under the age of 50 with a hematologic malignancy, whenever alternative therapies have a predicted probability of cure < 20%, and an HLA-matched related donor is available. BMT also may be indicated in other circumstances depending on the specific disease in question. The appropriate timing for SAA and CML is less problematic and has already been discussed (sec. 1.2, 1.3).

1.6.1. **Acute Myeloblastic Leukemia (AML)**. BMT is considered standard therapy for patients in their first chemotherapy-induced complete remission since it results in 50% long-term disease-free survival, compared to 20% for typical chemotherapy regimens. However, the best results from recent reports of chemotherapy indicate a similar disease-free survival to BMT [20, 21]. In addition, if BMT is delayed until the first sign of relapse, approximately 30% of patients still can be salvaged. Based on these considerations we believe that BMT is best performed at the initial relapse, rather than first remission, unless prognostic factors at diagnosis indicate a high risk of relapse. Adverse prognostic factors include secondary AML, antecedent hematologic

disorder, deletion of chromosome 5 or 7 (in whole or in part), trisomy 8, and certain chromosomal translocations, e.g., t(9;22). Patients in a second chemotherapy-induced remission (and those with more advanced disease) have little chance of cure and should be considered for BMT [22]. The most commonly used transplant regimens combine cyclophosphamide with TBI or busulfan, however, the high relapse rate (40% or more) following BMT for advanced leukemia indicates the need for more effective chemotherapy and immune modulation.

1.6.2. **Acute Lymphoblastic Leukemia (ALL)**. Current results of initial chemotherapy for ALL suggest that 80-90% of children and 40-50% of adults may be cured [13,23]. Many patients who relapse will respond to further chemotherapy, however, patients in a second chemotherapy-induced remission (and those with more advanced disease) have little chance of cure. A possible exception is patients who relapse after an initial remission of >18 months; of those who achieve a second complete remission 50% may be cured [24]. Based on these considerations we believe that BMT is best performed in first relapse, or second remission of ALL, unless prognostic factors at diagnosis indicate a high risk of relapse. Karyotype is the most important risk factor with the presence of any balanced translocation indicating an adverse prognosis [13,25]. Patients in a second relapse (and those with more advanced disease) have little chance of cure and also should be considered for BMT. The results of BMT for recurrent ALL indicate that 30-50% of patients can be expected to achieve long-term disease-free survival [11,26]. Again, the high relapse rate following BMT indicates the need for more effective chemotherapy and immune modulation.

1.6.3. **Myelodysplastic Syndrome (MDS), and Myeloproliferative Disorders**. BMT is the only therapy with the potential (although experience is still limited) for cure. Patients should be considered for BMT when the disease progression causes life-threatening complications [27,28].

1.6.4. **Lymphoma (including Hodgkin Disease and Intermediate or High-grade Non-Hodgkin Lymphomas)**. Conventional therapy is not effective for patients who fail aggressive combination chemotherapy for lymphoma, but approximately 25% can apparently be cured by BMT [12]. Many different BMT regimens have been used, without clear superiority of any one approach. The most frequent cause of failure is resistant disease. Patients who are refractory to standard therapy (having never achieved a complete remission) fare less well after BMT than patients who relapse from an initial response, and the best results are achieved in patients who relapse, but are still responsive to conventional agents. For patients like these, with "sensitive relapse", long-term disease-free survival can be expected in more than 40% [29]. Most of the lymphoma experience involves the use of autologous marrow, however some patients are not good candidates for autologous BMT because of poor marrow function, prior pelvic irradiation, or marrow lymphoma. In this situation allogeneic BMT may be the best choice. Thus for most patients BMT is recommended at the time of relapse from first-line combination chemotherapy. For patients with high-grade Non-Hodgkin lymphoma (lymphoblastic and small non-cleaved cell) prognostic factors have been identified that indicate a high risk of relapse (presence at diagnosis of bone marrow involvement accompanied by elevated serum LDH) and can be used to select patients who may benefit from BMT during first remission.

1.6.5. **Chronic Lymphocytic Leukemia, Waldenstrom's Macroglobulinemia, Low-grade Non-Hodgkin Lymphoma (NHL)**. These are chronic lymphoproliferative disorders for which there is no proven curative therapy, and despite their usually indolent course, most patients ultimately die of disease-related complications. There is limited experience with BMT in these disorders, but preliminary results are promising [30-32]. BMT should be considered for

younger patients (age < 55) with progressive or symptomatic disease after conventional therapy.

1.6.6 Patients with malignancies who would be treated with an autologous stem cell transplant but have a syngeneic donor.

1.7. Donors can be classified arbitrarily as "well-matched" or "partially-matched" based on the post-transplant risk of GvHD. Considering the three most important serologically-defined HLA loci (A, B, D) there are 6 possible alleles that can be matched. The DR locus has been further defined by molecular typing such that this technique has replaced serologic typing of the D region. DRB1 and DQB1 are two of the more defined regions that can be analyzed and matched for on a molecular basis. [33]

Well-matched donors carry the least risk of GvHD and are represented primarily by genotypically matched siblings (HLA 6/6). Although experience is more limited, similar results have been obtained with 5/6 HLA-matched family members and fully-matched (HLA 6/6) unrelated donors [34-36].

Partially-matched donors carry a greater risk of fatal GvHD (and possibly of graft rejection) and their use is only considered if no well-matched donor is available, autologous BMT is not possible, and the patient's underlying disease warrants the added risk. Included in this category are unrelated donors who are matched for class II specificities (HLA DRB and DQ), but mismatched for 1 HLA-A or B specificity, as well as family-member donors who are matched for 3 or 4 (of 6) HLA-A,B,D specificities. Patients who are ≤25 years of age may be considered for an unrelated transplant using a donor who is singlely mismatched at a Class I antigen. All other patients who do not have a fully matched unrelated donor will be treated on an appropriate cord blood protocol. The specifics matching criteria are contained in the BMT Standards of Therapy that are updated yearly.

For this study, bone marrow or blood progenitor cells (BPC) will be the primary source of hematopoietic stem cells . Bone marrow will be used for all standard risk patients, and blood progenitor cells will be used for all high risk patients with a fully-matched related donor, including MDS patients with > 10% blasts in the marrow [37-39]. Stem cells from an unrelated donor may be either bone marrow or blood progenitor cells, although it is preferred that standard risk patient receive bone marrow and high risk patients receive blood progenitor cells.

A syngeneic donor would be considered to have the same risk as an autologous stem cell transplant patient but because the donor is another individual, the patient would be treated on this protocol.

1.8. Transplant Conditioning Regimens (preparative regimens) – (see Section 5.2 for full dosing schema)

1.8.1. **CATG.** Published BMT data support the use cyclophosphamide 200 mg/kg and ATG 90 mg/kg for the treatment of aplastic anemia patients.
FluM. Recent evidence has shown that fludarabine at a dose of 125 mg/m^2 over 5days plus melphalan at a dose of 140 mg/m^2 over 2 days is a safe and potentially less toxic conditioning regimen in allogeneic transplant. Patients who are at higher risk for transplant-related toxicity will be treated with this regimen including older patients. [54, 55].

1.8.2. Patients who have undergone allogeneic or autologous transplant and fail to engraft or experience prolonged graft failure may be considered for a reinfusion of either: 1) donor lymphocytes, 2) previously harvested and stored stem cells, or 3) stem cells harvested from a suitably matched donor. In the third situation, the patient should receive additional

immunosuppression with Fludarabine 25 mg/m^2 intravenously every day for 5 days, and ATG 10 mg/kg/day intravenously every day for 4 days.

2. OBJECTIVES

2.1. The 2 major objectives are: 1) To study the morbidity, mortality and overall outcome of standard and novel conditioning regimens for the treatment of diseases by allogeneic BMT, and 2) To ensure that patients with uncommon diagnoses will be treated in a uniform fashion with the best therapy available.

2.2 For purposes of analysis, patients will be stratified into two groups (standard and high risk), since accrual of patients to some of the individual disease/status strata will be slow. The assignment of risk is as follows: (also, see section 4.3)

Standard risk:
- Acute leukemia, 1st CR
- Lymphoma, sensitive 1st relapse or 2nd remission
- CML, 1st CP
- MDS, untreated or Primary MDS with IPSS low or Intermediate grade 1 (see Appendix 6)
- AA with no co-morbidities *

High risk definition:
- Leukemia and lymphoma
  - 2nd CR or greater
  - Resistant 1st relapse
  - Primary refractory to standard chemotherapy (considered to be at highest risk)
- Previously treated MDS, Secondary MDS, or MDS converted to AML without induction therapy; with IPSS intermediate 2 or high risk (see Appendix 6)
- CML other than chronic phase 1
- High grade NHL in 1st CR
- AA with co-morbidities *
- Solid Tumors

*Co-morbidity is defined as a life threatening medical condition that is controlled with therapy (see Section 3.7)

2.3. Influence of donor histocompatibility on outcome will be examined by comparison of matched/related, mismatched/related (with or without T-cell depletion), and matched/unrelated transplants with stratification for type of preparative regimen.

2.4. Regimen selection will be based on criteria as indicated in the following table:

All patients with refractory disease will be treated as a first choice with FluM. If for any reason a patient is unable to be treated according to the table, the default will be FluM

Disease	**Risk**	**Age**	**HLA Match[1]**	**Regimen**	**Stem Cells[3]**
MDS					
	High	51-60	6/6 related	FluM	PBSC
	High	≤ 60	Unrelated	FluM	PBSC/BM
	High	≤ 50	5/6 related	FluM	BM
	Either	61-70	Related or Unrelated	FluM	PBSC/BM
	Either	>50	Syngeneic	FluM	PBSC/BM
AML					
	High	51-60	6/6 related	FluM	PBSC/BM
	High	31 - 60	Unrelated	FluM	PBSC/BM
	High	≤ 50	5/6 related	FluM	BM
	Either	61-70	Related or Unrelated	FluM	PBSC/BM
	Either	>50	Syngeneic	FluM	PBSC/BM
ALL	High	51-60	6/6 related	FluM	PBSC/BM
	High	17-50	5/6 related	FluM	BM
	High	≤ 41 - 60	Unrelated	FluM	PBSC/BM
	Either	60-70	Related or Unrelated	FluM	PBSC/BM
	Either	>50	Syngeneic	FluM	PBSC/BM
CML					
	High	≤ 60	Unrelated	FluM	PBSC/BM
	High	≤ 50	5/6 related	FluM	BM
	Either	60-70	Related or Unrelated	FluM	PBSC/BM
	Either	>50	Syngeneic	FluM	PBSC/BM
HD	High	< 70	6/6 related	FluM	PBSC/BM
	High	< 70	Unrelated	FluM	PBSC/BM
	High	< 50	5/6 related	FluM	BM
	Either	< 50	4/6	BuCATG	CB[4]
	Either	<70	Syngeneic	FluM	PBSC/BM
NHL					
	High	< 60	6/6 related	FluM	PBSC/BM
	High	< 60	Unrelated	FluM	PBSC/BM
	High	< 60	5/6 related	FluM	BM
	Either	60-70	Related or Unrelated	FluM	PBSC/BM
	Either	>50	Syngeneic	FluM	PBSC/BM
CLL	High	< 60	6/6 related	FluM	PBSC/BM
	High	< 50	5/6 related	FluM	BM
	High	< 60	Unrelated	FluM	PBSC/BM
	Either	60-70	Related or Unrelated	FluM	PBSC/BM

Disease	Risk	Age	HLA Match[1]	Regimen	Stem Cells[3]
	Either	<70	Syngeneic	FluM	PBSC/BM
AA	Either	< 60	6/6 related	CATG	PBSC/BM
	Either	60-70	Related or Unrelated	FluM	PBSC/BM
	Either	≤60	Syngeneic	CATG	PBSC/BM
	Either	>60	Syngeneic	FluM	PBSC/BM

1 An unrelated HLA A, B,or C mismatch, BM preferred over PBSC. Patients with single or greater HLA Antigen or Allele mismatch (at A, B, C, or DRB1) over 30 receive FluMel and Marrow as preferred conditioning regimen and stem cell source respectively. CB units should be 4/6 matches and preferably matched at HLA-DRB1.
FluM is the preferred regimen if there is any medical contraindication to a higher intensity regimen for PB or BM transplants. Patients must be transplanted from and identical twin sibling and be ≤60 years.

3 BM is preferred stem cell source for patients under the age of 18. If HLA-mismatched at HLA A or B antigen, Bone marrow is preferred. In HLA matched patients, PB is preferred for high risk BMT patients.

4 The CB cell dose must be 2 x 10^7 NC per kg minimum dose for a single unit. Cord Blood could be used as stem cell source with FluMel.

3.0 GENERAL ELIGIBILITY GUIDELINES

3.1. Diagnosis

3.1.1. severe aplastic anemia

3.1.2. chronic myelocytic leukemia

3.1.3. hematologic malignancy in first remission with high risk of relapse

3.1.4. hematologic malignancy in second or subsequent remission

3.1.5. hematologic malignancy, relapsed or refractory after first-line combination chemotherapy

3.1.6 myelodysplastic syndrome, untreated

1) with features of neutropenia and or blood product transfusion dependence

2) unfavorable cytogenetics

3) converted to AML without induction therapy

4) Intermediate 1 or higher IPSS (see Section 2.2, Appendix 5)

3.1.7 Solid tumor patients who would otherwise be treated on DS 91-15 (or equivalent autologous stem transplant protocol and have a syngeneic donor).

3.1.8 For myeloablative regimens
3.1.9 No KPS requirement for failure to engraft transplants and Reduced Intensity Conditioning with FluMel

3.2. Age $\geq 4, \leq 70$

3.3 Not pregnant

3.4. Required initial laboratory data
1. Pulmonary function tests (DLCO or DLVA) ≥50% predicted; DLCO to be corrected for hemoglobin or alveolar ventilation. (See Section 10.0 for pediatric requirements.)
2. Cardiac ventricular ejection fraction ≥50% by radionucleotide ventriculogram or echocardiogram.
3. Bili, Alk phos, SGOT < 3 x normal, unless due to disease
4. Creatinine clearance is ≥ 50 ml/min. (See Section 10.0 for pediatric requirements.)
5. HIV antibody negative
6. CMV and hepatitis status known; HBsAg negative

3.5. No serious organ dysfunction unless it is caused by the underlying disease; exclusion criteria include the following:
1. Uncontrolled or severe cardiovascular disease, including recent (< 6 months) myocardial infarction, congestive heart failure, symptomatic angina, life-threatening arrhythmia or hypertension
2. Uncontrolled bacterial, viral, or fungal infection
3. Uncontrolled peptic ulcer disease
4. Uncontrolled diabetes mellitus
5. Any severe pulmonary, hepatic, or renal disease, or any other condition which, in the opinion of the transplant director, would make this protocol unreasonably hazardous for the patient.

3.6. Compatible donor identified

3.6.1. Autologous BMT not possible or not desirable.

3.6.2. Well-matched donor: family member matched for 5 of 6 HLA specificities (A, B, DR); unrelated donor matched for HLA A, B, and DRB1 antigens. Patients may be singly mismatched at the A, B, C loci when using FluMel. Identical twin sibling.

3.6.3. All other patients are considered too highly mismatched and will be considered for cord blood transplant. CB must be a minimum of 2 x 10^7 NC per kg patient wt.

3.6.4. For this study, bone marrow or blood progenitor cells will be the primary source of hematopoietic stem cells.

3.7. Informed Consent: Patients must be aware of the neoplastic nature of their disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks and discomforts. There must be no other serious medical or psychiatric illness that would prevent informed consent.

4. REGISTRATION AND DATA SUBMISSION

4.1. Registration - to register patients, contact the BMT Coordinator. Transplant regimens will be assigned as per protocol guidelines by the BMT team.

4.2. Data pertaining to this protocol will be collected by the BMT research nurse, and/or any other persons assigned by the BMT department head.

4.3. Stratification by risk - for overall analysis of toxicity and response, patients will be assigned to one of two risk groups (refer to Section 2.2)

4.4 Reference Appendix 7 for definitions of On/Off Study Dates, Start/Stop Treatment Dates.

5. TREATMENT PLAN

5.1. **Pretransplant cytoreductive chemotherapy** may be administered to patients with relapsed or refractory disease in an attempt to demonstrate sensitivity to therapy and reduce bulky disease. The decision to treat and the choice of specific therapy to be used will be made on an individual case basis.

5.1.1. **Involved-field radiation therapy:** For all patients for whom radiation therapy is planned, it is recommended that radiation begin no sooner than 4 weeks and no greater than 8 weeks after transplant.

5.1.2. **Regimen selection** depends on diagnosis and prior therapy as defined in eligibility criteria (refer to table in Section 2.4)

5.1.3. **Stem Cell Infusion: Day 0** is the day on which the stem cells are infused. As required by scheduling, the stem cells may be infused on the same day after the last fraction of TBI is given. The described scheduling for each regimen is the preferred timing. However, it is recognized that situations may arise that require variation in scheduling. Any such deviation from described scheduling should be discussed with the Study Chair first.

The procedure of infusing stem cell products may be performed by the physician or qualified nurse under the direct supervision of a BMT physician. The stem cells are to remain sterile throughout the infusion process. All patients require continuous pulse oximetry monitoring during the procedure, with oxygen equipment available in the patient's room. All patients will have vital signs recorded before the procedure and at timed intervals during and after stem cell infusion. Emergency drugs, such as diphenhydramine, epinephrine, and corticosteroids will be available for use in appropriate doses. No other blood products should be given on the day of transplant, especially within 8 hours of planned infusion time.

Patients will be pre-medicated with the following medications (doses must be adjusted for pediatric patients):

1) Diphenhydramine (Diphenhydramine) 25 mg IV, 30 minutes prior to infusion of stem cells.
2) Lorazepam 0.5 mg IV, 30 minutes prior to infusion of stem cells.

For Recipients who are ABO incompatible with their donors, premedication will include:
1) Hyperhydration of 150 mls/m^2 per hour beginning 6-12 hours prior to infusion
2) Hydrocortisone 100 mg IV 15 minutes prior to infusion, and
3) Diphenhydramine 50 mg IV 15 minutes prior to infusion

Treatment of a transfusion reaction will include the following:
1) Stop infusion and give hydrocortisone 100 mg
2) Restart infusion as soon as patient is clinically stable

5.2. Transplant Conditioning Regimens (preparative regimens)

5.2.1. Cyclophosphamide, ATG summary:

Day	-5	-4	-3	-2	-1	0
C 50 mg/kg/2hr	X	X	X	X		
(total 200mg/kg)						
ATG* 30mg/kg/qd	X	X	X			
(total 90 mg/kg)						
Stem Cell Infusion						X

*ATG is given 4-8 hours after Cyclophosphamide, given via central line

Cyclophosphamide Diphenhydramine 25-50 mg IV should be given 30 minutes prior to the administration of all cyclophosphamide doses (adjusted for pediatric dosing). A minimum of 12 hours prior to first dose, begin IV hydration at 150 ml/m^2hr (see appendix 6). Cyclophosphamide, 50 mg/kg (ideal body weight or actual whichever is less) in 500ml D5W or NS, is given by 2-hr IV infusion (1200 -1400 hrs) days -5,-4,-3, and -2 (total dose 200 mg/kg). To calculate dose use IBW (see Appendix 1 for table of IBW by height) or actual weight, whichever is less. Hyperhydration is continued until 24 hrs. after the last cyclophosphamide dose. Lasix, 10-20 mg IV, will be given 2 hrs after each cyclophosphamide dose and then q4 hrs. prn to maintain urine flow >100ml/hr.

Antithymocyte Globulin (ATG) Prior to infusion of ATG patients will be premedicated with diphenhydramine 50 mg IV (adjust for pediatric dosing) and methylprednisolone 2 mg/kg IV . Four to eight hours after the completion of the first, second and third doses of Cyclophosphamide, ATG 30 mg/kg (actual body weight) will be given intravenously over 4-8 hours.

5.2.2. Fludarabine, Melphalan summary:

Day	-6	-5	-4	-3	-2	-1	0
Flu 25 mg/m^2 qdx5	X	X	X	X	X		
(total 125 mg/m^2)							
M 70 mg/m^2 qd x2				X	X		
(total 140 mg/m^2)							
Stem Cell Infusion							X

Fludarabine. A minimum of 1 hour prior to first dose, begin IV hydration. Fludarabine, 25 mg/m^2 (see appendix 6) (actual body weight) in 100 ml D5W or NS, is given by 30-minute IV infusion days -6, -5, -4, -3, and -2 (total dose 125 mg/m$^{2)}$.

Melphalan. Prepare melphalan 70 mg/m^2 BSA (see appendix 6) (actual body weight) in diluent provided at a final concentration not to exceed 5 mg/ml to infuse over 1/2 hr following fludarabine, day -3 and -2 (total dose 140 mg/m$^{2)}$. On day -3 hydrate 150cc/m^2/hr IV hydration 1 hour prior to Melphalan. Hyperhydration is continued until 24 hrs. after last melphalan dose.

5.2.3. **Fludarabine, ATG summary:** (FOR GRAFT FAILURE ONLY)

Day	-5	-4	-3	-2	-1	0
FLU 25 mg/m^2 qdx5	X	X	X	X	X	
(total 125 mg/m^2)						
ATG 10 mg/kg/day qdx4	X	X	X	X		
(total 40 mg/kg)*						
Stem Cell Infusion						X

steroid premedication of 2 mg/kg/day medrol (pre ATG)

Fludarabine. A minimum of 1 hour prior to first dose, begin IV hydration. Fludarabine, 25 mg/m^2 (actual body weight) in 100 ml D5W or NS, is given by 30-minute IV infusion days -5, -4, -3, -2, -1 (total dose 125 mg/m$^{2)}$.

Antithymocyte Globulin (ATG) Prior to infusion of ATG patients will be premedicated with diphenhydramine 25-50 mg IV and methylprednisolone 2 mg/kg IV. ATG will be given within one hour of the completion of the first, second, third, and fourth doses of Fludarabine, ATG 10 mg/kg (actual body weight) will be given intravenously over 4-8 hours.

6. DRUG FORMULATION, AVAILABILITY AND PREPARATION

6.1. **Cyclophosphamide** is commercially available in 100, 200, 500, 1000, 2000 mg vials. Dilute with 5, 10, 25, 50 ml, or 100 ml respectively, of NS (normal saline) for Injection, yielding a

concentration of 20 mg/ml which is stable for 24 hours at room temperature. Give the appropriate IV dose by 2 hour IV infusion after further dilution to 500 ml with D5W.

6.2. **Antithymocyte globulin** (ATGAM, Upjohn) is commercially available in 5 ml ampules containing 50 mg of horse gamma globulin/ml. It should be stored in a refrigerator (2-8°C). It should be diluted in 0.9% NaCl to a concentration not exceeding 4 mg/ml, and is stable for 24 hours when diluted. The final product is filtered. ATG should be administered alone.

6.3. **Melphalan** is commercially available in 50 mg vials. It is to be admixed just prior to intravenous administration and is stable for 90 minutes. The dose of melphalan will be diluted with the diluent that is provided with the product to a final concentration of 5 mg/ml and protected from light.

6.4 **Fludarabine** is commercially available in 50 mg vials. It is reconstituted by adding 2 ml of sterile water for injection to provide a solution containing 25 mg/ml which is stable for 8 hours at room temperature.

7.0 POTENTIAL TOXICITY - MANAGEMENT AND DOSE MODIFICATIONS

7.1. **Toxicity Grading** - The Bearman Toxicity Criteria, Appendix 2) will be used for the grading and reporting of all toxicities. Grade 4 hematosuppression does not have to be reported for agents known and expected to cause hematosuppression at the dose used. Bearman Toxicity Criteria refers to **regimen-related toxicity only**. GvHD grading is located in Appendix 4 **.**

7.2. **Hematologic**: Two to four weeks of severe pancytopenia (PMN < 500/μL, Platelets < 20,000/μL) are expected, and rarely patients may fail to engraft. All blood products will be irradiated (2500 cGy) to prevent graft vs. host disease. Despite optimal antibiotics, 10-15% of patients treated with intensive chemotherapy may die as a result of infection. Infection prophylaxis and treatment will be given according to standard accepted medical practice. On rare occasion, we may transfuse granulocytes from an acceptable donor for the purpose of treating a life-threatening infection in a neutropenic patient. With prophylactic platelet transfusions, the risk of death from hemorrhage is <5%. Use of T-depleted marrow may delay recovery and increase the risk of graft failure to as much as 10%.

7.3. **Hepatic**: Moderate toxicity is common. More severe, possibly fatal, liver toxicity can occur, usually in the form of veno-occlusive disease. With the study regimens the incidence of fatal liver toxicity should be < 10%. Management of liver toxicity is with standard supportive and symptomatic measures. Avoid exposure of patients to other hepatotoxic agents whenever possible.

7.4. **Pulmonary**: Idiopathic interstitial pneumonitis (IP) is possible after high dose alkylating agent therapy or TBI. With the study regimens the risk of fatal idiopathic IP is felt to be < 10%. Patients with diffuse pulmonary infiltrates often present a difficult diagnostic and management problem. Whenever possible, histologic confirmation of the diagnosis should be attempted by bronchoalveoar

lavage, or transbronchial or open-lung biopsy to exclude infectious causes, including cytomegalovirus.

7.5. **Cardiac**: High-dose cyclophosphamide can produce fatal hemorrhagic pancarditis. The risk of fatal cardiac toxicity with the study regimens is <5%. Patients who develop signs of congestive heart failure not attributable to fluid overload should be evaluated for signs of carditis before additional Cyclophosphamide is given. Studies should include ECG (to compare voltage to pretreatment ECG), radionuclide ventriculogram, and/or echocardiography. If evidence of pericarditis, pericardial effusion or impaired myocardial function (decreased ejection fraction) is found, no further chemotherapy will be administered. In this situation patients must be watched carefully for signs of pericardial tamponade; pericardiectomy may be required.

7.5.1. Fludarabine can cause weakness, paresthesias or peripheral neuropathies, visual or auditory impairment, and/or mental status changes such as confusion, agitation, depression, or coma.

7.5.2 Some antibiotics, which may be needed to treat infections during the period of low white blood cell counts, can cause eighth cranial nerve damage resulting in hearing loss (especially high-frequency tones) and dizziness which may be permanent. To minimize this possibility, antibiotic levels will be monitored.

7.6. **Genitourinary**:

7.6.1. Urinary metabolites of cyclophosphamide can produce hemorrhagic cystitis. Microscopic hematuria is common following high-dose Cyclophosphamide regimens and up to 20% of patients may have gross hematuria or symptoms. Vigorous hydration of patients (3,000 ml/m2/day) prior to beginning Cyclophosphamide and continuing until 24 hours after the final Cyclophosphamide dose produces a dilute urine and reduces the likelihood of severe cystitis. The risk of life-threatening cystitis is estimated to be <1%. For patients with a history of previous cyclophosphamide induced hemorrhagic cystitis, MESNA may be used.

7.7. **Renal**: All these agents in high doses can produce renal toxicity that can be minimized by vigorous hydration and avoidance of concomitant exposure to other nephrotoxic agents. Kidney damage is usually reversible, but severe cases may require dialysis. Carboplatin in high doses can produce renal toxicity which can be minimized by vigorous hydration and avoidance of concomitant exposure to other nephrotoxic agents.

7.8. **Gastrointestinal**:

7.8.1. Nausea/Vomiting - Many patients will experience moderate to severe toxicity. All patients should receive vigorous antiemetic treatment

7.8.2. Stomatitis/Dysphagia - Many patients will experience severe toxicity. Adequate pain relief often requires parenteral narcotics.

7.8.3. Diarrhea - Most patients will experience moderate-severe diarrhea which responds to standard symptomatic therapy. Appropriate studies are needed to exclude infectious causes of diarrhea, especially C. difficile.

7.9. **Skin**: Generalized erythroderma can occur with painful palms and soles and superficial desquamation at sites of mechanical trauma. Topical steroid creams may provide symptomatic relief. Severe cases may require a brief course (3-5 days) of systemic corticosteroids. Long-lasting hyperpigmentation may follow resolution of the erythroderma.

7.10. **Hair**: All patients will experience total (reversible) alopecia.

7.11. **Graft vs. Host Disease**: Approximately 80% of patients will exhibit some manifestation of GvHD. Severe GvHD may occur in up to 40% of patients with an overall mortality of 20% due to GvHD and its complications. The risk of severe or fatal GvHD is increased for older patients and for patients receiving marrow from partially matched donors. A chronic form of GvHD is expected to occur in up to 40% of patients who survive beyond 3 months; 10% may experience significant disability due to chronic GvHD that persist for months to years post-transplant. Measures for prevention and treatment of GvHD will be followed as per standard practice. Acute GVHD should be treated according to existing BMT SOPs (http://internal.roswellpark.org/files/1_2_1/Internal/patient_care/bmt/2002Clinical/CP2002.03.doc)

7.12 **Allergy:** Antithymocyte globulin may be associated with a serum sickness like reaction consisting of rash, hives, pruritis, joint aches. More severe anaphylactic like reactions with the development of bronchospasm and anaphylactic shock are uncommon but reported after the use of ATG. Prior to administration patients should be premedicated with Diphenhydramine and Methylprednisolone. Epinephrine and resuscitation equipment must be available during administration of ATG. Other chemotherapeutic agents may be associated with mild allergic reactions including rash, hives, itching nasal stuffiness, sinus congestion, sneezing, watery eyes, and running nose occur occasionally; more severe reactions with low blood pressure and wheezing are rare.

7.13. **Bone marrow and/or blood stem cell infusion of a previously frozen product:**
In certain cases, stem cells may have been previously cyropreserved for use. Products are protected from damage during freezing with DMSO (dimethylsulfoxide). DMSO produces a garlic-like odor on the breath that lasts for 1 to 2 days. In rare instances, severe allergic reaction to DMSO may occur. Red coloration of urine may be noticed for 1 to 2 days after the reinfusion due to the release of hemoglobin from blood cells in the marrow damaged by freezing.

7.14. **Secondary malignancy**: Exposure to alkylating agents and radiation increases the risk of developing leukemia or a second cancer.

7.15In summary, **overall day 100 transplant related mortality** is expected to be approximately 20-30% due to graft failure, regimen-related organ toxicity, infection, hemorrhage, and graft versus host disease. Risk factors associated with higher transplant related mortality include increased patient age, prior chemotherapy, poor performance status, unrelated donor transplant, and more intensive transplant regimens.

8.0 DATA AND SAFETY MONITORING PLAN

The Principal Investigator (PI) will be responsible for continuous monitoring of the safety of the study. (see section 12.3.2 for stopping rules)

Patient Outcomes Rounds are held weekly on the transplant unit, at which time all BMT patient care is reviewed, including:

- medications (chemotherapy for conditioning regimens; prophylactic, empiric and therapeutic antimicrobials; graft-versus-host disease prophylactic and therapeutic medications; and possible drug interactions).
- adverse events and/or adverse reactions to any medication, procedure, or other treatment; reports are filed according to RPCI policy and procedure.
- regimen-related toxicity, based on Bearman toxicity grading, and/or Common Toxicity Criteria (CTC) if the toxicity does not correlate with a Bearman grade.
- indications for additional testing or therapies such as biopsies, scans or xrays.
- a properly signed and dated transplant consent.
- compliance issues that could compromise patient safety; pretransplant, a conference is held for all allogeneic patients for the purpose of describing the need for allogeneic patients to obtain lodging within a 30 mile radius of the hospital and to have a caregiver present at all times while the patient is an outpatient. In addition, psychosocial evaluations are completed on all allogeneic and high-risk autologous transplant patients prior to transplant, to identify any compliance issues.
- other aspects of safety monitoring as prescribed by the BMT Standards of Care and common clinical practice. These include daily physical examinations, clinical laboratory testing, routine surveillance cultures, therapeutic drug level monitoring (i.e., Vancomycin, Tacrolimus, Tobramycin, Cyclosporine). Patients who have been discharged from the hospital are monitored in the BMT Clinic until all transplant-related issues are resolved and they are returned to the care of their referring physicians.
- Assignment of KPS/Lansky Score (Appendix 6)

The BMT Quality Assurance plan requires quarterly reporting to the BMT Quality Assurance Committee, which in turn reports to the hospital Quality Assurance Committee. Indicators for BMT patient safety monitoring include:

- Patient complaints
- Adverse events and serious adverse events
- Bearman and CTC toxicity grades 3 and 4
- Variances in the delivery of standard care
- Readmissions prior to day +100 post transplant
- Deaths occurring prior to day +100 post transplant
- Engraftment

Followup on all transplant patients is continued even after they have returned to the care of the referring physicians. A Long Term Transplant Clinic has been established, which provides care for allogeneic patients with chronic complications, as well as assessments to identify dental, bone, and psychosocial complications.

All outcomes are reported to the International Bone Marrow Transplant Registry (IBMTR), and/or the National Marrow Donor Program (NMDP). Registry reports are reviewed internally prior to

submission to the respective registry. These data are also entered into the RPCI BMT Database, from which patient outcomes are assessed and reviewed on a regular basis. Regimen-related toxicities reported in this fashion have resulted in a number of changes to transplant protocols since 1997, thus decreasing toxicity and improving outcomes in a number of patient groups.

Registry reports also establish the efficacy of treatment as measured by overall best response to transplant at day +100 and on subsequent annual reports. The patients' medical records serve as original source documents for all reporting. Audits are conducted every two to three years by the IBMTR and the NMDP.

9. REMOVAL OF PATIENTS FROM PROTOCOL THERAPY AND TOXICITY REPORTING:

9.1. **Removal from protocol**. If the constraints of this protocol are detrimental to the patient's health, the patient will be removed from the protocol. In this event the reason for withdrawal will be documented. Patients will be taken off study after a minimum of 4 years of follow up.

9.2. **Toxicity Reporting**

9.2.1. **Expected toxicity** (recorded in protocol consent form or manufacturer's literature). Within 10 days of occurrence written reports should be submitted to the IRB and the protocol chairman in the following circumstances (Bearman and CTC toxicity)

9.2.2. **Unexpected toxicity**

All instances of Bearman grade 3-4 will be reported to the IRB and the protocol chairman immediately by telephone and followed by a written report

Grade 3-4 acute GVHD will be reported by written notification.

Failure to engraft (defined as a patient alive on day 45 with no ANC recovery)

Graft failure (defined as a patient who had initial ANC recovery but subsequently had a decline in ANC that required additional stem cell support)

Death due to any cause
Readmission due to any reason up to 100 days post BMT.

10. REQUIRED DATA

Record on the flow sheets:

1. Important hematologic recovery endpoints
   day PMN >500/µL, >1000/µL; Plt >25K, >100K; Hb >10gm%
   day of last Plt transfusion, last RBC transfusion
2. day(s) of occurrence of severe toxicity (gr3)

Test/Observations	Pre-Rx	Post-Rx***	Post-Disch
Signed Consent Form	x	--	--
Ht/Wt/BSA	x	--	--
Ideal Body Wt/Adjusted Body Wt (if applicable)	x	--	--
Serology (Infectious disease screening)	x	--	--
HLA–Class I and II typing	x	--	--
Cr Clearance*****	x	--	--
PFT's/DLCO/DLVA****	x	--	--
MUGA or ECHO	x	--	--
EKG	x	--	--
Quantitative IG's	x	--	--
BM aspirate, biopsy*	x	d+100 for all d+30 for any not in marrow remission prior to transplant	as clinically indicated
Prophylactic IT Chemo	x	after d+100	as clinically indicated
Staging profile**	x	repeat positive studies d+100 and d+360; then as clinically indicated	repeat positive studies d+100 and d+360; then as clinically indicated
Flow cytometry analysis testing on donor and recipient	x		
Chimerism (obtain samples from donor and recipient pre-transplant)	x		
Lymphoid and myeloid chimerism	x	d+30, d 60, d 100	as clinically indicated
Flow Cytometry BMT Standard of Care	x	d+30, d 100, d 180, d 360	as clinically indicated
CBC/Plt	x	q day to PMN>500, Plt>20K, then as clinically indicated	q wk to day 30
Urinalysis	x	as clinically indicated	--
PT-INR	x	as clinically indicated	--
Full Chemistry Panel	x	biw	as clinically indicated
Chest X-ray******	x	as clinically indicated	--
Performance Status	x	qwk	as clinically indicated
Toxicity (Bearman and CTC)	--	weekly	q l mo until d 100

§ d 0 is day of marrow transplant; studies to be obtained as close to indicated time as possible
* Obtain cytogenetics if previously abnormal
** Non-invasive studies including: (1) measurement (perpendicular diameters) of palpable disease, (2) CT scan of chest, abdomen, pelvis, (3) Whole-body Ga scan (SPECT, if available)
*** Post therapy is defined as until engraftment and /or discharge from hospital.
Intervals shown are the minimum requirement
****Not required in pediatric patients <5 years, 5-8 years to be done at WCOB, >8 years to be done at RPCI.
*****In pediatric patients, only if CARBO Regimen or Serum creatinine – Abnormal.
******Not required for Pediatric patients unless has pulmonary problems for pneumonia.

11. RESPONSE CRITERIA

11.1 **Complete Response**:

11.1.1. **Lymphoma**. Disappearance of all measurable disease, signs, symptoms, and biochemical changes related to the tumor, for ≥4 weeks, during which no new lesions may appear.

Complete Response Undetermined (CRU): Complete disappearance of all known disease for ≥4 weeks, with the exception of persistent scan abnormalities of unknown significance.

11.1.2. **Leukemia**: Remission marrow status with no evidence of prior disease. Patients with a cytogenetic abnormality must also have normal karyotype.

11.2. **Partial Response**:

11.2.1. **Lymphoma**: A reduction of > 50% in the sum of the products of the perpendicular diameters of all measurable lesions lasting > 4 weeks, during which no new lesions may appear and no existing lesion may enlarge.

12. STATISTICAL CONSIDERATIONS

12.1. **Study Design**:

This is a phase II-III study of high dose therapy and allogeneic blood or marrow transplantation for patients with severe aplastic anemia, and patients with hematologic malignancy who have failed standard first-line chemotherapy or who are in their first remission, but are at high risk of relapse. Patients will be stratified into two groups in the following manner: (1) High risk - patients with progressive disease at the time of transplant, including those who failed to achieve a complete remission with first-line therapy, and those who have relapsed and failed to respond to further treatment (2) Standard risk - leukemia patients transplanted in first remission, lymphoma patients transplanted in sensitive first relapse or second remission, patients with CML in chronic phase, untreated aplastic anemia patients, and untreated or primary MDS patients. Response rates for each regimen will be determined separately for the two strata. Patients with solid tumors will be evaluated in an exploratory fashion.

12.2. **Endpoints**:

The primary objective of this study is to determine the activity of the proposed blood or marrow transplant regimens. Response rates and toxicities will be reported using descriptive statistics. The Kaplan-Meier method will be used to construct progression-free, and overall survival curves. Patients will be stratified into standard vs. high-risk groups. The BMT conditioning regimens will be compared within each risk group on toxicity, efficacy, progression-free survival and overall survival. Toxicity criteria for premature termination autologous SCT will be applied for syngeneic transplants.

12.3. **Sample Size**:

12.3.1. Patients will be differentially accrued to two risk strata: high-risk and standard-risk for disease relapse. It is expected that the standard-risk stratum will have an overall efficacy rate (post-BMT CR rate) of 70% and the high-risk strata will have an overall efficacy rate (post-BMT CR rate) of 50%. The two-sided alpha error is set at 0.02 to correct for multiple comparisons. For the standard-risk strata, 55 patients will be registered for each regimen to be able to detect a 20% difference in efficacy between regimens with power>0.90. For the high-risk strata, 70 patients will be registered for each regimen to be able to detect a 20% difference in efficacy between regimens with power>0.90. Accrual is expected at 55 patients per regimen times 5 regimens for the standard-risk strata and 70 patients per regimen times 5 regimens for the high-risk strata, yielding a total protocol accrual of 625 patients. Approximately 100 patients will be accrued every three years.

12.3.2. Entry of patients will be terminated before full accrual if treatment-related deaths occur at an unacceptable rate. A sequential stopping rule will be used. If the number of toxic deaths (regimen-related) exceeds the number in the table below at any given point, accrual will be suspended for that regimen and the toxicity will be deemed unacceptable. This stopping rule is based on a sequential probability ratio test with one-sided type I and type II error rates set at alpha = 0.01 and beta = 0.01, and the null and alternative toxicity rates set at $Po \leq 0.20$ and $P_1 > 0.20$. If the observed number of toxic deaths is greater than or equal to the number in the table, then one may conclude with 99% power that the toxic death rate is greater than an unacceptable rate of 20% and the study should be stopped.

No. Patients	6	12	18	24
Unacceptable No.	4	6	8	11

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Appendix 1

Calculation of Ideal and Adjusted Body Weight

To calculate ideal body weight for men:

50 + 0.91x(height in cm – 152)

To calculate ideal body weight for women:

45 + 0.91x(height in cm – 152)

To calculate ideal body weight for small children: ages 1-16 and under 5 feet (152.5 cm)

$$\frac{(\text{Height in cm})^2 \times 1.65}{1000}$$ gives you IBW in kg.

.

To calculate ideal body weight for children: ages 1 – 16 and 5 feet tall and taller

IBW (male) = 39 + (2.27 X height in inches over 5 feet)

IBW (female) = 42.2 + (2.27 X height in inches over 5 feet)

To calculate adjusted ideal body weight for men and women:

Ideal body weight + [0.25 x (actual body weight – ideal body weight)]

The calculation of ideal body weight is referenced in the package insert of Busulfex® (busulfan) Injection, and also found in the article written by: Gibbs, JP, Gooley, T, Comeau, B, et al, "The Impact of Obesity and Disease on Busulfan Oral Clearance in Adults", *Blood*, Vol 93, No 12 (June 15) 1999: pp 4436-4440.

Appendix 2

Regimen Related Toxicity in Patients Undergoing BMT (Bearman*)

	Grade I	Grade II	Grade III
Cardiac	Mild EKG abnormality, not requiring medical intervention; or noted heart enlargement on CXR with no clinical symptoms	Moderate EKG abnormalities requiring and responding to medical intervention; or requiring continuous monitoring without treatment; or congestive heart failure responsive to digitalis or diuretics	Severe EKG abnormalities with no or only partial response to medical intervention; or heart failure with no or only minor response to medical intervention; or decrease in voltage by more than 50%
Bladder	Macroscopic hematuria after 2 days from last chemotherapy dose with no subjective symptoms of cystitis and not caused by infection	Macroscopic hematuria after 7 days from last chemotherapy dose not caused by infection; or hematuria after 2 days with subjective symptoms of cystitis not caused by infection	Hemorrhagic cystitis with frank blood, necessitating invasive local intervention with installation of sclerosing agents, nephrostomy or other surgical procedure
Renal	Increase in creatinine up to twice the baseline value (usually the last recorded before start of conditioning)	Increase in creatinine above twice baseline but not requiring dialysis	Requirement of dialysis
Pulmonary	Dypsnea without CXR changes not caused by infection or congestive heart failure; or CXR showing isolated infiltrate or mild interstitial changes without symptoms not caused by infection or congestive heart failure	CXR with extensive localized infiltrate or moderate interstitial changes combined with dyspnea and not caused by infection or CHF; or decrease of PO2 (>10% from baseline) but not requiring mechanical ventilation or > 50% O2 on mask and not caused by infection or CHF	Interstitial changes requiring mechanical ventilatory support or >50% oxygen on mask and not caused by infection or CHF
Hepatic	Mild hepatic dysfunction with bili > 2.0 mg% but < 6.0 mg %; or weight gain > 2.5 % and < 5 % from baseline of noncardiac origin; or SGOT increase more than 2-fold but less than 5-fold from lowest preconditioning	Moderate hepatic dysfunction with bili >6 mg% < 20 mg %; or SGOT increase with > 5-fold from preconditioning; or clinical ascites or image documented ascites > 100ml; or weight gain > 5% from baseline of noncardiac origin	Severe hepatic dysfunction with bili > 20 mg %; or hepatic encephalopathy; or ascites compromising respiratory function
CNS	Somnolence but the patient easily arousable and oriented after arousal	Somnolence with confustion after arousal; or other new objective CNS symptoms with no loss of consciousness not more easily explained by other medication, bleeding, or CNS infection	Seizures or coma not explained by other medication, CNS infection, or bleeding
Stomatitis	Pain and/or ulceration not requiring a continuous IV narcotic drug	Pain and/or ulceration requiring a continuous IV narcotic drug	Severe ulceration and/or mucositis requiring preventive intubation; or resulting in documented aspiration pneumonia with or without intubation
GI	Watery stools > 500 ml but < 2,000 ml every day not related to infection	Watery stools > 2,000 ml every day not related to infection; or macroscopic hemorrhagic stools with no effect on cardiovascular status not caused by infection; or subileus not related to infection	Ileus requiring nasogastric suction and/or surgery and not related to infection; or hemorrhagic enterocolitis affecting cardiovascular status and requiring transfusion

NOTE: Grade IV regimen-related toxicity is defined as fatal toxicity

*Bearman Sl et al. Regimen Related Toxicity in Patients Undergoing Bone Marrow Transplantation. JCO 1988, 6(10); 1562-1568

Appendix 3

Criteria For Acute Graft-Vs-Host Disease

Clinical staging of acute graft-vs- host disease according to organ involvement

STAGE	SKIN	LIVER	INTESTINAL TRACT
0	No rash	Bilirubin < 2.0 mg/dL < 34µmol/L	Diarrhea 500 ml/day
+	Maculopapular rash <25% of body surface	Bilirubin 2-2.9 mg/dL 34-50 µmol/L	Diarrhea 500-1000 ml/day
++	Maculopapular rash 25-50% of body surface	Bilirubin 3.0-6.0 mg/dL 51-102 µmol/L	Diarrhea 1000-1500 ml/day
+++	Generalized erythroderma	Bilirubin 6.1-15 mg/dL 103-255 µmol/L	Diarrhea 1500 ml/day
++++	Generalized erythroderma with bullous formation and desquamation	Bilirubin > 15 mg/dL > 255 µmol/L	Severe abdominal pain with or without ileus

Clinical grading of severity of acute graft-vs- host disease

GRADE	DEGREE OF ORGAN INVOLVEMENT
I	+ to ++skin rash; no gut involvement; no liver involvement; no decrease in clinical performance
II	+ to +++ skin rash; + gut involvement or + liver involvement (or both); mild decrease in clinical performance
III	++ to +++ skin rash; ++ to +++ gut involvement or ++ to ++++ liver involvement (or both) marked decrease in clinical performance
IV	Similar to Grade II with ++ to ++++ organ involvement and extreme decrease in clinical performance

Source: Thomas et al, N Engl. J Med. 1975; 292, 832

Appendix 4

International Prognostic Scoring System (IPSS) For MDS Classification

		IPSS Score	**Value**		
Prognostic Variable	0	0.5	1.0	1.5	2.0
BM Blasts (%)	<5	5-10	-	11-20	21-30
Karyotype*	Good	Intermediate	Poor		
Cytopenias**	0/1	2/3			

* Cytogenetic Classification
Good: normal, or –Y alone, del(5q) alone or del(20q) alone
Poor: complex (≥3 abnormalities) or chromosome 7 anomalies
Intermediate: other abnormalities, +8

** Cytopenias were defined as:
Hemoglobin <10 g/dL
ANC <1,500/μL
Platelet Count <100,000/ μL

Scores for risk groups are as follows:

Score	Risk	Median Survival	AML Evolution*
0	Low	5.7 yrs	9.4 years
0.5-1.0	Intermediate 1	3.5 yrs	3.3 years
1.5 –2.0	Intermediate 2	1.2 yrs	1.1 years
> 2.5	High	0.4 yrs	0.2 years

* Time until 25% of patients in the risk group developed acute myeloid leukemia. AML, acute myeloid leukemia

Adapted from Greenberg P, Cox C, Le Beau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes, Blood 89:2079-2088,1997. erratum: Blood 91: 1100, 1998.

Appendix 5

Calculation of Body Surface Area

The "New England Journal" formula for calculating body surface area (BSA) in adults will be the standard method at Roswell Park Cancer Institute.

To calculate Body Surface Area: **Square root ((wt[kg] x ht[cm])/(3600))**

Performance Status

Karnofsky Performance Status (age>=16 years		Lansky Scale (age <16 years)	
Able to carry on normal activity; no special care is needed:		**Normal Range.**	
100	Normal; no complaints; no evidence of disease	100	Fully active
90	Able to carry on normal activity	90	Minor restriction in physically strenuous play
80	Normal activity with effort	80	Restricted in strenuous play, tires more easily, otherwise active
Unable to work; able to live at home, care for most personal needs; a varying amount of assistance is needed:		**Mild to moderate restriction**.	
70	Cares for self; unable to carry on normal activity or to do active work	70	Both greater restrictions of, and less time spent in, active play
60	Requires occasional assistance but is able to care for most needs	60	Ambulatory up to 50% of time, limited active play with assistance/supervision
50	Requires considerable assistance and frequent medical care	50	Considerable assistance required for any active play; fully able to engage in quiet play
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly:		**Moderate to severe restriction.**	
40	Disabled; requires special care and assistance	40	Able to initiate quiet activities
30	Severely disabled; hospitalization indicated, although death is not imminent	30	Needs considerable assistance for quiet activity
20	Very sick; hospitalization necessary	20	Limited to very passive activity initiated by others (i.e., TV)
10	Moribund; fatal process progressing rapidly	10	Completely disabled, not even passive play

Appendix 6

Definitions: On/Off Study Dates, On/Off Treatment Dates

On-Study Date	Start Treatment Date	Stop Treatment Date	Off-Study Date
Date conditioning regimen started	Date conditioning regimen started	Date infusion of stem cells is complete (relevant for patients who have more than one infusion over 2 or more days)	Date of first disease progression post-transplant or date of death due to any cause or date patient failed to engraft

** All >/=2nd BMTs and DLIs count toward accrual, except for planned tandem auto BMTs which count once toward accrual