# WVU1909

# UNRELATED UMBILICAL CORD BLOOD (UCB) TRANSPLANTATION

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## UNRELATED UMBILICAL CORD BLOOD (UCB) TRANSPLANTATION

### TABLE OF CONTENTS




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## 1.0 OBJECTIVES

1.1 To assess the outcome including disease-free survival, overall survival, and treatment-related mortality in patients with hematologic malignancies treated with umbilical cord blood (UCB) transplantation

1.2 To evaluate engraftment and the rate of hematopoietic recovery

1.3 Evaluate donor-recipient chimerisms

1.4 To determine the incidence and severity of acute and chronic graft-versus-host disease (GVHD)

## 2.0 BACKGROUND AND RATIONALE

Allogeneic hematopoietic cell transplantation (allo- HCT) is a curative therapy for the treatment of hematological and non-hematological malignancies and certain non-malignant conditions. Bone marrow or peripheral blood from an HLA matched sibling donor is the most commonly used source of allogeneic stem cells. However, HLA matched siblings are available for less than one third of the patients who require allo- SCT. In the absence of an HLA matched sibling, volunteer unrelated donors or partially mismatched related donors (PMRD), stored cord blood may be used as a source of allogeneic stem cells. Stored cord blood has been used as a source of allogeneic stem cells in infants and children, but had early skepticism in adults because of concerns about the engraftment potential of the relatively limited number of stem cells. The number of stem cells in a unit of cord blood is generally one log less than the number of stem cells on an average collection of bone marrow from an adult for transplantation.

### 2.1 Advantages and disadvantages of using cord blood as a source of stem cells.

There are many potential advantages of using cord blood as a source of allogeneic stem cells. It is a readily available source and umbilical cord units can be harvested at no risk to the mother or child since it is post-delivery. Collection of marrow from unrelated donors is commonly a lengthy process. Cord blood is available on demand and avoids delays in treatment for patients with unstable disease. Cord blood is less likely to be exposed to infectious agents, especially viruses such as CMV that result in an inferior outcome after allogeneic stem cell transplantation. The risk of severe acute graft versus host disease (GVHD) may be less after cord blood transplantation in comparison to volunteer unrelated donor transplantation. Up to a two antigen mismatch may be tolerated without a significant effect on the overall transplant outcome, expanding the patient population who may undergo allogeneic transplant. For patients who lack an HLA matched bone marrow donor, cord blood from an unrelated donor is an alternative source of hemopoietic progenitor cells.

The major disadvantage of cord blood transplantation is the slow rate of hematopoietic recovery and relatively higher incidence of failure to engraft. This delay of recovery may result in a higher incidence of infectious complications in the early post transplant period. Lack of donor lymphocytes for future use is another major disadvantage with cord blood transplantation.[1,2]

### 2.2 Results of cord blood transplantation in children and adults

In a retrospective analysis from the Eurocord and International Bone Marrow Transplantation Registry, the long-term survival after transplantation from cord blood was similar or superior to survival after transplantation of marrow when the donor is a sibling.[3] Also, Eurocord analysis revealed that children

with acute leukemia who received bone marrow, marrow depleted of T cells, or HLA mismatched cord blood transplantation from unrelated donors had similar survival.[4] The cause of death was different in different groups. There were early deaths from delayed engraftment in the groups that received cord blood, more relapses in the group that received T cell depleted bone marrow, and more cases of GVHD in the group that received unmanipulated marrow. In a matched pair analysis from the University of Minnesota, the survival after transplantation of unrelated donor cord blood was found to be comparable to HLA matched unrelated donor marrow transplantation in children. Despite increased HLA disparity in the cord blood group, GVHD was similar in both groups. Donor derived engraftment of 88% at day 45 was not statistically significant in difference compared to engraftment rate in the marrow group (96%).[5]

Rocha et al.[6] compared cord blood versus bone marrow transplant for patients with acute leukemia. There were 98 patients who received cord blood and 584 patients who received bone marrow. Cord blood recipients were younger, weighed less, and had more advanced disease at the time of transplant. Bone marrow recipients were all 6/6 HLA matches, whereas 94% of cord blood recipients had an HLA-incompatible graft [5/6 (51%), 4/6 (39%), and 3/6 (4%)]. Cord blood recipients were shown to have lower risks of grade II, III, or IV acute GVHD (relative risk, 0.57; P=0.01), but delayed neutrophil recovery (relative risk, 0.49; P<0.001). There was no significant difference in chronic GVHD, transplant-related mortality, relapse rate, and disease-free survival.

Laughlin et al.[7] also compared cord blood versus bone marrow transplant in patients with leukemia. The cord bloods were mismatched at one HLA antigen (34pts) or two HLA antigens (116pts). The bone marrow patients were HLA matched (367pts) or had one HLA mismatch (83pts). The cord blood recipients were younger and had more advanced disease. As expected, cord blood recipients had a slower hematopoietic recovery. Acute GVHD was higher in patients receiving bone marrow and chronic GVHD was higher in patients receiving cord blood. Mismatched bone marrow transplant and mismatched cord blood showed similar rates of treatment-related mortality, treatment failure, relapse rate, and overall mortality.

Reduced-intensity BMT has become more appealing as an attempt to minimize the toxicity and mortality of the preparative regimen while maintaining the anti-leukemic activity of the transplanted immune system. This approach may also offer some benefit in cord blood transplant, considering a major barrier is the delay in neutrophil recovery. Using a lower intensity regimen should allow some recipient neutrophils to persist during the engraftment phase. One example of this approach was published by Barker et al[8] who utilized two regimens: fludarabine, busulfan, total body irradiation (Flu/Bu/TBI) and fludarabine, cytoxan, and total body irradiation (Flu/Cy/TBI). Sustained donor engraftment was 76% with Flu/Bu/TBI and 94% with Flu/Cy/TBI. The median day of neutrophil recovery was 26 and 9.5 days, respectively between the two regimens. Incidence of grades III-IV GVHD was 9% and 1 year survival was 39%. Numerous other centers have successfully utilized a reduced intensity approach in cord blood transplantation.[9-14] Despite the possible advantages of reduced-intensity conditioning, a recent publication by the Minnesota group has shown higher relapse risk in the patients treated with a reduced-intensity regimen as compared to a more standard myeloablative regimen.[17] We have amended our protocol to allow an ablative preparative regimen for patients who can tolerate them, due to this data.

2.3 Cord blood banking

After the success of the first allogeneic umbilical cord blood transplantation in 1988, programs for banking screened unrelated donor CBSC have been initiated both in the United States and Europe. Dr Pablo Rubenstein started the first such bank at the New York Blood Center (NYBC) in 1993. Since its inception, the NYBC has provided unrelated donor cord blood stem cells for over 1000 transplants. Analysis of outcomes for the initial 562 transplant recipients from the NYBC revealed a cumulative rate

of engraftment of 81% by day 42 for PMNs. and 85% by day 180 for platelets.[15] Currently approximately more than 100,000 cord blood units are available in cord blood banks worldwide and more than 2000 patients have received cord blood transplants from these banks. Netcord, an international cooperative group of cord blood banks, has developed a detailed set of standards for cord blood banking to facilitate international exchanges and to guarantee the quality of these products.

## 3.0 STUDY DESIGN

### Cord Blood Unit Selection

UCB units will be required to be a 4/6 to a 6/ 6 HLA A, B , DRB1 antigen match with the patient as allowed per NMDP guidlines. A minimum total nucleated cell (TNC) dose of >2.0 x $10^7$/kg at the time of freezing will be utilized when possible. When using double units, each unit should contain a minimum pre-cryopreserved TNC dose of 1.5 x $10^7$/kg.

### UCB Transplant Procedure

There will be a myeloablative and reduced-intensity preparative regimen that can be given prior to infusion of cord product. The myeloablative approach will be selected in younger patients (≤50yo) with a HCT-CI score <3. The reduced-intensity regimen will be selected for all older patients (>50) or younger patients with a HCT-CI score ≥3. The reduced-intensity regimen will also be chosen for any patients being transplanted for indolent/follicular lymphomas, CLL, myeloma, or Hodgkin lymphoma; irrelevant of age or HCT-CI score. On a case by case basis, patients may receive a preparative regimen outside of their designated category as noted above with the approval of the PI, if deemed in the patient's best interest. Example: A patient that is 55yo with high-risk AML and a HCT-CI score 1, may be approved for the myeloablative preparative regimen..

Myeloablative Preparative Regimen:

- Fludarabine 40 mg/m2 IV on Days -6, -5, -4, and -3
- Busulfan 130mg/m2 IV on Days -6, -5, -4, and -3
- TBI 200cGy on Day -1
- Thymoglobulin (rabbit ATG) 1.5mg/kg IV Days -4, -3, -2 (may be given at the discretion of treating physician)

Reduced-intensity Preparative Regimen:

- Cyclophosphamide 50mg/kg IV Day -6
- Fludarabine 40 mg/m2 IV Days -6, -5, -4, -3, -2
- TBI 200cGy on Day -1
- Thymoglobulin (rabbit ATG) 1.5mg/kg IV Days -4, -3, -2 (may be given at the discretion of treating physician)

The preparative regimen will be followed by infusion of one or two UCB unit(s). UCB unit(s) will be thawed according to methods of Rubinstein et al.[16] If two products are used, they will be administered sequentially on the same day 1-6 hours apart. Tacrolimus and mycophenolate mofetil (MMF) will be used for GVHD prophylaxis. On day +30, +60, +100, +180, and +365 the chimeric status of patients will be interpreted by VNTR analysis. Immune reconstitution (Digeorge Panel) will also be checked at these time points.

**The parameters to be monitored are:**

1) TNC dose
2) $CD34^+$ cell dose
3) Degrees of donor-recipient chimerism by VNTR analysis (to be collected approximately on day +30, +60, +100, +180 and +365) using peripheral blood.
4) Neutrophil recovery (first day of ANC >0.5 x $10^9$/l for 3 consecutive days).
5) Platelet recovery (days to platelet count of 20 x $10^9$/l and 50 x $10^9$/l, without platelet transfusion within 7 days).
6) Incidence and severity of acute GVHD.
7) Incidence and severity of chronic GVHD.
8) Disease-free survival and overall survival.
9) Transplant related mortality before and after day 100.
10) Cause of death
11) Immune reconstitution (to be collected approximately on day +30, +60, +100, +180 and +365)

## 4.0 ELIGIBILITY

### 4.1 Inclusion criteria

4.1.1 Age: 16-70 years
4.1.2 Available 4/6, 5/6, or 6/6 HLA antigen match (using A,B, and DRB1) cord blood unit
4.1.3 ECOG performance status of 0-2 (Karnofsky ≥ 70%)
4.1.4 Serum bilirubin <2 x upper limit of normal
4.1.5 Serum creatinine < 2 mg/dl
4.1.6 DLCO or FEV1 ≥50% predicted
4.1.7 Left ventricular ejection fraction ≥ 35%
4.1.8 No uncontrolled infection
4.1.9 If female, not pregnant
4.1.10 Informed consent given
4.1.11 No major organ dysfunction precluding transplantation.

4.1.12 One of the following malignancies or bone marrow failure syndromes:

a) Chronic myelogenous leukemia (CML)
b) Acute myelogenous leukemia (AML)
c) Myelodysplastic syndrome
   Intermediate or high risk disease by prognostic scoring system
d) Multiple myeloma
e) Hodgkin lymphoma
f) Non-Hodgkin lymphoma
g) Chronic lymphocytic leukemia (CLL)
h) Acute lymphocytic leukemai (ALL)
i) Severe Aplastic Anemia

### 4.2 Exclusion criteria

4.2.1 Patient pregnant
4.2.2 Age <16, >70

4.2.3 ECOG performance status of >2 (Karnofsky < 70%)
4.2.4 Psychiatric disorder or mental deficiency of the patient sufficiently severe as to make compliance with the BMT treatment unlikely, or making informed consent impossible
4.2.5 Serum bilirubin ≥ 2 x upper limit of normal, transaminases >3x upper limit of normal
4.2.6 Serum creatinine ≥ 2mg/dl
4.2.7 DLCO <50% predicted
4.2.8 Left ventricular ejection fraction <35%
**4.2.9** Major anticipated illness or organ failure incompatible with survival from BMT

## 5.0 PATIENT CLINICAL EVALUATION

### 5.1 Pre-transplant patient evaluation per BMT SOPs, including the following:

5.1.1 HLA typing
5.1.2 Chimerism assay (VNTR analysis)
5.1.3 Blood typing (ABO, Rh)
5.1.4 Bone marrow biopsy, chromosome analysis, molecular analysis and flow cytometry
5.1.5 Disease staging (see Appendix I).
5.1.6 Antibody screen for HBV, HCV, HIV, HTLV I/II, CMV, EBV, syphilis (VDRL or RPR)
5.1.7 CBC with differential, coagulation screen, chemistry profile
5.1.8 Serum pregnancy test, if female with child-bearing potential
5.1.9 Pulmonary function tests and DLCO
5.1.10 Cardiac function: EKG and MUGA scan or Echocardiogram
5.1.11 Nutritional assessment
5.1.12 Dental assessment
5.1.13 Ophthalmology assessment
5.1.14 Informed consent signed

### 5.2 Follow Up to Day 180

Disease staging on day +100, or earlier if clinical suspician of relapse. Disease assessment testing varies with disease, see Appendix I for appropriate testing.

Peripheral blood will be drawn and/or bone marrow aspirate will be taken approximately on day +30, +60, +100 +180 and +365 to assess for degrees of donor-host chimerism using VNTR. Peripheral blood is the preferred sample, but if WBC is not adequate, bone marrow aspirate sample may be used. Immune reconstitution will also be monitored at these time points.

### 5.3 Beyond Day 180

After 6 months, patients will be off the clinical protocol and will be monitored per standard BMT SOP's. Physical exam, CBC and complete blood chemistry testing will be done to monitor patient's condition. Additional testing not already mentioned in the protocol such as chest x-ray, CT and PET scans, disease staging studies, pulmonary function testing will be performed as necessary based on individual patient conditions and will be at the discretion of the investigator.

## 6.0 PATIENT TREATMENT PLAN

### 6.1 Pre-transplant treatment

Eligible patients may receive appropriate chemotherapy according to standard indications to control malignancy prior to the preparative regimen.

### 6.2 Central Venous Catheter Placement

Appropriate central venous access will be obtained pre-transplant. A triple-lumen Hickman catheter is preferred.

### 6.3 Infection Prophylaxis/Empiric Anti-infective Therapy

WVU BMT SOP for infection prophylaxis and empiric anti-infective therapy in allogeneic HSCT recipients will be followed. Patients will receive prophylaxis as follows:

- Antiviral: Acyclovir 400mg PO (or IV) q12hrs starting at beginning of preparative regimen, continuing until Day +365 or longer if still receiving immunosuppressants. CMV and EBV will be monitored weekly (every Monday) for reactivation by PCR analysis.
- Antifungal: Fluconazole 400mg PO Daily starting Day -2 until Day +100
- Antibacterial: Levofloxacin 500mg PO Daily starting Day -2 until ANC>500 post-nadir
- PCP prophylaxis will start at the time of engraftment (ANC >500 post-nadir) with Bactrim DS qMWF until Day +180 or longer if still receiving immunosuppressants.
- Growth Factors: Filgrastim 5mcg/kg subcutaneously daily starting Day +5 until ANC>1,500 post-nadir.

### 6.4 Preparative regimen

Myeloablative Preparative Regimen:

- Fludarabine 40 mg/m2 IV on Days -6, -5, -4, and -3
- Busulfan 130mg/m2 IV on Days -6, -5, -4, and -3
- TBI 200cGy on Day -1
- Thymoglobulin (rabbit ATG) 1.5mg/kg IV Days -4, -3, -2 (may be given at the discretion of treating physician)

OR

Reduced-intensity Preparative Regimen

- Cyclophosphamide 50mg/kg IV Day -6
- Fludarabine 40 mg/m2 IV Days -6, -5, -4, -3, -2
- TBI 200cGy on Day -1
- Thymoglobulin (rabbit ATG) 1.5mg/kg IV Days -4, -3, -2 (may be given at the discretion of treating physician)

### 6.5 UCB Infusion

UCB unit(s) will be thawed according to methods of Rubinstein et al.[16] If two products are used, they will be administered sequentially on the same day 1-6 hours apart.

### 6.6 GVHD Prophylaxis

- Tacrolimus 0.03 mg/kg/day PO or 0.015mg/kg/day IV starting Day -3 to Day +180, with dosage adjustments to maintain appropriate levels.

- MMF 15 mg/kg PO BID, with dose rounded to the nearest 250mg beginning day -3 to Day +30, then tapered until Day +60.

### 6.7 Transfusion support

Leukocyte reduced and irradiated blood products. CMV negative recipients to receive CMV safe blood products.

### 6.8 Hospital Discharge

Patient will be admitted to the hospital for approximately 6 weeks and will be discharged when he/she fulfills criteria per BMT SOPs.

## 7.0 MANAGEMENT OF POST TRANSPLANT COMPLICATIONS

The major complications of allogeneic transplantation are CMV reactivation, acute and chronic GVHD, disease progression, graft failure and opportunistic infection (bacterial/ fungal). Patients with these complications will be treated following WVU BMT SOPs.

## 8.0 HAZARDS AND DISCOMFORTS

Allogeneic HSCT is a complex procedure associated with a significant bone marrow failure, morbidity, and mortality. Patients eligible for this protocol will all have a life threatening hematologic malignancy for which allogeneic HSCT has shown to be the only treatment with curative potential. The exact incidence of hazards and discomforts is highly variable, and depends on factors like age, disease status, degree of HLA matching, CMV serostatus, etc. The following is an incomplete list of hazards and discomforts:

Occurring uniformly in all patients:

1. Alopecia (reversible)
2. Nausea and vomiting, ranging in severity from grade 1 to grade 4
3. Grade 4 anemia, neutropenia and thrombocytopenia
4. Mucositis, ranging in severity from grade 1 to grade 4
5. Ovarian/testicular ablation resulting in long-term (irreversible) sterility

Occurring in > 25% of all patients:

1. Acute GVHD ranging in severity from grade I to grade IV
2. Infection, ranging in severity from grade 1 to grade 4
3. CMV reactivation
4. Chronic GVHD, ranging in severity from limited to extensive
5. Cataract formation

Rare (<10%), but potentially lethal complications:

1. Veno Occlusive Disease of the liver
2. Cardiac arrhythmias and congestive heart failure

3. Pulmonary hemorrhage
4. TTP/HUS

## 9.0 WITHDRAWAL FROM THE PROTOCOL

**Withdrawal from the transplant procedure**
Patients will be given ample time to withdraw from the protocol prior to admission for transplant. Thereafter, the nature of the procedure does not permit safe withdrawal from the protocol.

## 10.0 RESPONSE CRITERIA AND EVALUATION OF RESULTS

### 10.1 End Points

Tumor regression, acute and chronic GVHD, transplant-related mortality (TRM), disease-free survival, overal survival, degrees of marrow chimerism and graft failure.

### 10.2 Tumor response criteria

Varies by disease (See Appendix I)

## 11.0 STATISTICAL CONSIDERATIONS

### 11.1 Study Design

The study is a Phase II, non-randomized, single-center trial.

### 11.2 Accrual

It is estimated that we will accrue 1 to 5 patients per year on this protocol.

### 11.3 Randomization

There is no randomization aspect to this trial.

### 11.4 Analysis of Outcomes

Engraftment: defined as neutrophil recovery associated with donor engraftment within the first 60 days after transplant.

Overall Survival: Overall survival at day 180 after transplant.

### 11.5 Interim Analysis and Stopping Guideline

Interim analyses for safety will be conducted after every fifth patient in each regimen, reaches the 180 day post-transplant time point, for the first 15 patients in each regimen. A goal engraftment rate will be $\geq$70% and a goal overall survival rate will be $\geq$40%. The study will be evaluated for termination if:

- After 5 patients, if none survive or $\leq$1 have engrafted
- After 10 patients, if $\leq$2 survive or $\leq$4 have engrafted
- After 15 patients, if $\leq$4 survive or $\leq$8 have engrafted

## 12.0 FINANCIAL CONSIDERATIONS

Coverage for the procedure will be by patient insurance approval.

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## Appendix I: Disease Staging and Response Definitions

### Staging

1. CML

a. Bone marrow aspiration and biopsy

b. Cytogenetics

c. BCR/ABL gene rearrangement by PCR

2. AML, MDS

a. Bone marrow aspiration and biopsy

b. Cytogenetics

c. Disease-specific translocation by PCR (if available)

3. Multiple myeloma

a. Bone marrow aspiration and biopsy

b. M-protein measurement (SPEP or 24 hour urinary light chain excretion light chain disease)

c. SIEP, UIEP

4. NHL, HD, CLL (only tests that were abnormal initially, unless otherwise indicated)

a. Physical exam

b. CT scans

c. Bone marrow aspiration and biopsy

d. Cytogenetic analysis

e. Disease-specific translocation by PCR (if available)

### Response Definitions

1. CML

a. Complete response (CR): Resolution of bone marrow and blood morphologic abnormalities and absence of Philadelphia chromosome by standard cytogenetic analysis.

b. Partial response: Reduction in percentage of Philadelphia chromosome positive metaphases by > 50% without disappearance of positive metaphases.

c. Molecular complete remission: In addition to criteria above for complete remission, BCR/ABL rearrangement by RT-PCR is absent.

2. AML

a. Complete response: Resolution of abnormal blood and bone marrow morphology with less than 5% blasts and resolution of disease-specific chromosome abnormality (if present) by standard cytogenetic analysis.

b. Partial response: Decrease in bone marrow and peripheral blood blast count by ≥ 50%.

c. Molecular complete remission: In addition to criteria above for a complete response, disease-specific rearrangement is absent by PCR analysis.

3. MDS

a. Complete response: Resolution of abnormal blood and bone marrow morphology with less than 5% blasts and resolution of disease-specific chromosome abnormality (if present) by standard cytogenetic analysis.

b. Partial response: Decrease in bone marrow and peripheral blood blast count by ≥ 50%.

**c.** Molecular complete remission: In addition to criteria above for a complete response, disease-specific rearrangement is absent by PCR analysis.

4. Multiple myeloma

a. Complete response: Bone marrow less than 5% plasma cells, polytypic by immunohistology, and absence of M-protein on electrophoresis and immunoelectrophoresis.

b. Partial response: Reduction in M-protein by ≥ 50%.

5. NHL, HD, CLL

a. Complete response: Resolution of disease by physical findings and normalization of all previously abnormal clinical tests such as bone marrow examination and computed tomographic scans (CT). In addition, resolution of disease-specific chromosome abnormality (if present) by standard cytogenetics.

b. Partial response: Reduction in disease volume in all measurable sites by $\geq$ 50%**,** using product of diameters.

c. Molecular complete remission: response above in addition rearrangement by PCR analysis.

**APPENDIX II: GVHD Grading Scale**

**1. Acute GVHD**

a. If patient develops acute GVHD at any time after BMT, acute GVHD is graded as outlined below.
b. If patient dies before day 30 and has not developed acute GVHD, then the patient is considered not evaluable for GVHD.

Clinical Stage of Acute GVHD according to Organ System

| Stage | Skin | Liver | Intestine |
|---|---|---|---|
| + | Maculopapular rash < 25% of body surface | Bilirubin 2-3 mg/dl | >500-1000 ml diarrhea /day or nausea, anorexia or vomiting with biopsy (EGD) confirmation of upper GI GVHD |
| ++ | Maculopapular rash 25-50% if body surface | Bilirubin 3-6 mg/dl | >1000-1500 ml diarrhea/day |
| +++ | Maculopapular rash . 50% of body surface area or generalized erythroderma | Bilirubin 6-15 mg/dl | >1500 ml diarrhea/day |
| ++++ | Generalized erythroderma with bullous formation and desquamation | Bilirubin > 15mg/dl | >1500 ml diarrhea/day plus severe abdominal pain with or without ileus |

Overall Clinical Grading of Severity of Acute GVHD

| Grade | Skin | Liver | Gut |
|---|---|---|---|
| I | 1-2 | 0 | 0 |
| II | 0<br>0<br>1-3<br>1-3<br>1-3<br>3 | 0-1<br>1<br>0-1<br>1<br>0<br>X | 1<br>0-1<br>1<br>0-1<br>0<br>X |
| III | 0-3<br>0-3<br>0-3 | 2-3<br>0-3<br>4 | 0-2<br>2-3<br>0-3 |
| IV | 0-3<br>4 | 0-4<br>0-4 | 4<br>0-4 |

**2. Chronic Graft-vs.-Host Disease**

a. If patient develops chronic GVHD at anytime after BMT, chronic GVHD is graded as outlined below.

b. If the patient dies before day 100 and has not developed chronic GVHD, then the patient is considered not evaluable for chronic GVHD.

• Limited chronic GVHD

<u>Either or both</u>

- Localized skin involvement

- Hepatic dysfunction due to chronic GVHD

• Extensive chronic GVHD

Either

- Generalized skin involvement, or
    - Localized skin involvement and/or hepatic dysfunction

Plus

- Liver histology showing chronic aggressive hepatitis, or
- Involvement of eye (Schirmers test with less than 5mm wetting), or
- Involvement of minor salivary glands or oral mucosa demonstrated on labial biopsy, or
- Involvement of any other target organ