# UNIVERSITY OF MINNESOTA BONE MARROW TRANSPLANTATION PROTOCOL

# AUTOLOGOUS TRANSPLANTATION FOR MULTIPLE MYELOMA

**MT2003-13**


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Protocol Changes

| Version Date | Summary of Changes | Consent change |
|---|---|---|
| 3/23/2017 | Updated study committee; Section 3: updated eligibility criteria to conform to current standard practice; Section 6.1 updated timing of disease staging; added ECOG performance status to Appendix 1 | 3/23/2017 |
| 03/13/2015 | throughout protocol: remove dexamethasone and thalidomide maintenance – change to maintenance as medically appropriate per institutional guidelines<br>update event reporting to the IRB's current requirements | yes |
| 08/14/2014 | increase enrollment goal to 250 patients | Yes |
| 03/11/2010 | Section 3 - Change upper age for eligibility from 70 years to 75 years, delete creatinine clearance requirement; section 4 designate current treatment plan as for patients with GFR ≥ 30 ml/min and add a new treatment plan for patients with GRF < 30 ml/min; updated response criteria to International Uniform Criteria (now appendix II); Section 4.1 clarify mobilization details for patients who achieve as CR, CR, VGPR and for those with GFR < 30 ml/min; section 4.2 add treatment modifications for patients with GFR < 30 ml/min; Update protocol to current format and template language adding administrative sections (registration, conduct of study, data and safety monitoring plan); update SAE language to current Cancer Center and IRB reporting requirements; add Performance Status as appendix I, move response criteria to appendix II | |
| 10/17/2008 | Added Dr. McClune to study committee and removed Dr. Barker; section 4.1.2 added adjusted body weight formula for melphalan dosing； removed research blood sample collection; | |
| 10/18/2005 | Adjusted ideal body weight dosing formula added to clarify Cyclophosphamide /Mesna doses. Section 4.0 | 11/1/2005 |
| 6/22/2005 | Section 3.0 All patients with multiple myeloma requiring therapy will be eligible for this study (previously only stage 2 and 3 patients were eligible).<br>Section 4.1.2.4 clarification of melphalan hydration<br>Section 4.1.5 clarification of zolendronic acid dosing | |
| 10/12/04 | Clarified that eligibility is for patients < **or equal to** 70 years of age<br>Dr. Mukta Arora takes over as Principal Investigator | |
| 8/6/04 | Clarified Allopurinol start date is day –3, not day –4 (for consistency across myeloma protocols (4.1.2.3) | |
| 5/3/04 | Clarified that pre-transplant G-CSF is 10μg/kg/d (and post transplant is 5μg/kg/d) | |

## 1.0 OBJECTIVES

In order to improve disease control and extend disease free survival in patients with multiple myeloma, the study is designed to answer the following questions:

1.1 Can high dose melphalan followed by reinfusion of PBSC induce complete response in a large proportion of treated patients in conjunction with rapid hematologic recovery, modest length of hospitalization and modest transplant associated morbidity and mortality.

1.2 Can maintenance therapy with thalidomide + dexamethasone prevent or delay malignant relapse for patients achieving significant cytoreduction post transplant (removed effective March 13, 2015).

## 2.0 BACKGROUND AND RATIONALE

Multiple myeloma is a malignant proliferation of plasma cells producing marrow infilteration, osteolytic bone lesions and immunodeficiency and which despite multiagent combination chemotherapy, is not curable with conventional therapy. However, multiple myeloma is frequently responsive to high dose chemotherapy, with improved responses and extended survival being seen with myelosuppressive doses[1,2,3,4]. Currently high dose therapy followed by autologous or allogeneic bone marrow transplant (BMT) has become a common treatment for multiple myeloma.

2.1 Results of allogeneic BMT suggest that alloimmune antitumor reactivity may provide long term disease control. Unfortunately, conventional approaches to allografting are complicated by 30- 40% TRM[5]. The inability of myeloma patients to tolerate allografting may relate to an inability of generally elderly and immune suppressed patients to tolerate the combined effects of high-dose therapy and allografting. In addition allogeneic BMT is appropriate for only one third of patients who have a matched sibling donor while alternative donor allotransplants have not been fully explored in patients with myeloma.

2.2 Autologous BMT offers lower associated morbidity and mortality (<5%) and additionally has the advantages of being suitable for all patients with viable hematopoeitic cells available for harvest and cryopreservation and for older patients. Extensive cumulative experience has been reported with median overall and disease free survival of 43-68[1-3,5-7] and 21-43 months[1,2,6], respectively. However, it is associated with a continuing and nearly universal risk of disease progression and relapse. Sixty four patients underwent autologous transplantation for multiple myeloma from 1993 to 2002 at the University of Minnesota. In these, a complete response rate of 33% at 1 year and median overall and disease free survival of 53 months and 29 months respectively, were observed.

2.3 In order to improve autologous transplant results, post transplant therapies such as interferon[8,9] and the anti-angiogenesis agent thalidomide[10-13] are being used. Dexamethasone, an effective agent in myeloma, has been combined with thalidomide resulting in synergy and no unexpected toxicities[14]. Initial results suggest the

combination of thalidomide and dexamethasone is well tolerated after autologous transplantation[15]. (This was removed with the March 13 2015 revision)

2.3.1 Strategies to prevent relapse have included various post transplant maintenance therapies. Of these interferon is the most extensively studied. A moderately sized retrospective EBMT study demonstrated a longer median progression-free survival (29 vs 20 months, p = 0.006) and longer overall survival (78 vs 47 months, p= 0.007) in patients receiving post transplant interferon[9]. A small randomized trial showed a non-statistically significant trend to longer progression free survival with interferon but no improvement in overall survival[8]. The University of Minnesota's experience with post-autotransplant interferon showed a trend towards superior progression-free survival in patients using post-transplant interferon, however the medication could be initiated in only 54% of the patients. Despite these results, interferon is not consistently used post transplant, largely because of toxic side effects.

2.3.2 Other agents used include pulse high dose corticosteroids, usually dexamethasone. In the conventional chemotherapy setting, these have favorably impacted survival, but have only recently been explored post transplant[16].

2.3.3 Thalidomide inhibits angiogenesis in animal models and is active in myeloma with response rates of 30% even in patients with advanced and refractory disease[10]. Thalidomide also, in pre-clinical studies, inhibits the production of IL-6 by peripheral blood mononuclear cells[11,17]. Data suggest that IL-6 production by marrow stromal cells is important in the pathogenesis of MM[17]. Thalidomide has been used concomitantly with corticosteroids without the occurrence of unexpected toxicities and with possible synergistic effects[12]. The optimal dose of thalidomide is not established, although toxicities are dose-related. Responses are reported even at 50 mg/day. Current trials generally target the maximum tolerated dose up to a daily dose of 200 mg/day[13].

2.3.4 In this treatment plan, maximum clinical response and a setting of minimal residual disease will be achieved with chemotherapy and subsequent transplantation. Thalidomide + dexamethasone will then be employed as maintenance therapy (deleted with the March 13 2015 – maintenance per section 5) . Patients enrolled in the trial may have received thalidomide as part of their initial therapy or as salvage therapy with or without a response prior to transplant. Absence of a response pre transplant may be secondary to a high tumor burden at initiation of therapy. In the post transplant setting with a reduced tumor burden, thalidomide in combination with dexamethasone may improve complete response rate and delay relapse. With this integrated therapeutic plan, we hope to improve the treatment results and survival for patients with myeloma and additionally to monitor critical parameters of the transplant treatment course.

2.3.5 The major clinical outcome in this trial will be the percent of patients achieving complete response (CR) to the therapy plan. The second major endpoint will be the extended disease-free survival. Secondary endpoints will include: overall survival, transplant-related mortality, incidence of relapse and disease progression, hematologic recovery, time to progression and relapse, time to attainment of CR and CR+PR, duration of maintenance treatment, drop-out rate from maintenance treatment, incidence of toxicities and incidence of infections.

## 3.0 PATIENT SELECTION AND REGISTRATION

Study entry is open to adults regardless of gender or ethnic background. While there will be every effort to seek out and include women and minorities, the patient population is expected to be no different than that of other multiple myeloma studies at the University of Minnesota.

- Patients meeting the Durie and Salmon criteria for initial diagnosis of multiple myeloma, requiring therapy and meeting one of the following:
    - After initial therapy in either first complete or partial remission or no objective response
    - After achieving initial response and later disease progression, patient will be eligible after subsequent therapy upon achievement of either complete or partial response
- Is not eligible or has refused any protocols of higher priority
- 18 - 75 years of age
- Patients will be ineligible if they have advanced myeloma refractory to salvage chemotherapy regimens.
- Adequate organ function defined as:
    - Hematologic: hemoglobin ≥ 8 gm/dl (untransfused), WBC ≥ 3000/µl, absolute neutrophil count (ANC) ≥ 1500/µl, platelets ≥ 100,000/µl (untransfused)
    - Cardiac: no active ischemia by ECG or clinical symptoms, left ventricular ejection fraction ≥40% by either MUGA scan or echocardiogram. If EF is <50%, a Cardiology consult should be placed and echocardiogram performed if not already done.Hepatic: bilirubin < 2.0 mg/dl, ALT < 3x the upper limit of normal
    - Pulmonary: FEV1 AND FVC >50% predicted and DLCO (corrected) > 50% predicted; if the corrected DLCO is not able to be calculated, PI must be contacted.Performance status: Eastern Cooperative Group Performance (ECOG) or Karnofsky Performance Status (KPS) of 0-1 or ≥80%, respectively; if KPS is decreased due to myeloma, ≥70% is acceptable (Appendix I)
    - (appendix I).
- Free of active uncontrolled infection at the time of study entry.
- Patients must be ≥ 2 weeks (minimum) to 4 weeks (preferred) from prior myelosuppressive chemotherapy (primarily lenalidomide) to facilitate mobilization.
- Female patients who are pregnant (positive β-HCG) or breastfeeding will be excluded from study entry. Sexually active men and women must use contraceptive techniques during and for 4 weeks following completion of maintenance therapy
- Patients must exercise informed voluntary consent and sign a consent form approved by the University of Minnesota IRB: Human Subjects Committee.

**Patient Registration**
Registration will occur after the patient has signed the subject consent and eligibility is confirmed, but before any treatment has been administered. To be eligible for registration to this study, the patient must meet each criteria listed on the eligibility checklist based on the eligibility assessment documented in the patient's medical record. Upon completion of the screening evaluation, eligibility confirmation and obtaining written consent, the study coordinator or designee will enroll the patient into ONCORE.

## 4.0 TREATMENT SCHEMA

**Targeted days may be altered as clinically appropriate.**

**For patients with GFR ≥ 30ml/min**

| MM meeting eligibility criteria |
|---|
| Peripheral blood stem cell mobilization<br>GCSF alone<br>or<br>Cyclophosphamide 4gm/$m^2$ + Mesna* followed by<br>G-CSF 10µg/kg/d.<br>Collect PBSC daily x 3-4 days when ANC > 700/µl.<br>Target cell dose 5.0 x $10^6$ CD34 cells / kg |
| **Autologous PBSC Transplant**<br>High-dose Melphalan (200 mg/$m^2$)<br>+ ≥2x$10^6$ CD34 cells/kg |

**For patients with GFR < 30ml/min: All patients to be assessed in nephrology clinic prior to transplant**

| MM meeting eligibility criteria |
|---|
| Peripheral blood stem cell mobilization<br>GCSF alone<br>or<br>Cyclophosphamide 4gm/$m^2$ + Mesna* followed by<br>G-CSF 10µg/kg/d.<br>Schedule 6 hour hemodialysis run to begin 14 hours after completion of 2 hour cyclophosphamide infusion<br>Collect PBSC daily x 3-4 days when ANC > 700/µl.<br>Target cell dose 5.0 x $10^6$ CD34 cells / kg |
| **Autologous PBSC Transplant**<br>High-dose Melphalan (140 mg/$m^2$) |

| |
|---|
| + ≥2x$10^6$ CD34 cells/kg<br>Consider addition of palifermin i.v. 60mcg/kg/day for 3 consecutive days before and after melphalan (total 6 doses)<br>First 3 doses given on -6,-5,-4 in clinic (melphalan on day -2)<br>Last 3 doses given 0, +1, +2 |

*The dose of Cyclophosphamide and Mesna will be based on patient's weight using the following guideline:

For patients ≤150% of his/her ideal body weight, the dose will be based upon actual body weight (ABW)
For patients > 150% of his/her ideal body weight, the dose will be based upon adjusted ideal body weight (AIBW).
The following formulas will be used

Males IBW= 50 kg + 2.3 kg/inch over five feet
Females IBW = 45.5 kg + 2.3 kg/inch over five feet

Adjusted Ideal Body Weight Formula:
AIBW=IBW + [(0.5) x (ABW – IBW)]

4.1 Peripheral blood stem cell (PBSC) mobilization.

After eligible patients have been completely staged and exercised consent, their disease status will assessed. If patients achieve a sCR, CR or VGPR then they may receive G-CSF mobilization alone per institutional guidelines. For patients who fail G-CSF mobilization, chemomobilization with cyclophosphamide may be attempted.

In patients who do not achieve a CR: proceed with cyclophosphamide mobilization: one cycle of chemotherapy and growth factor to effect cytoreduction and mobilization of PBSC for collection.

- Day 1: Cyclophosphamide 4gm/$m^2$ intravenously (i.v.) over 2 hours. Mesna 800mg/ $m^2$ IV x 5 doses will be given preceding and then 3 hours, 6 hours, 9 hours, and 12 hours following the cyclophosphamide.
  In patients with severe renal dysfunction (GFR≤30 ml/min)[21], this will be modified as follows:
  - A temporary hemodialysis line will be required.
  - Cyclophosphamide will be given at full dose unless requiring adjustment for obesity
  - Administer cyclophosphamide as 2 hour infusion
  - MESNA 800 mg/$m^2$ iv loading dose followed by a 24 hour continuous infusion.
  - Schedule a 6 hour hemodialysis run to begin 14 hours after completion of 2 hour cytoxan infusion

- Day 4 (72 hours after Cyclophosphamide): Begin granulocyte colony stimulating factor (G-CSF) G-CSF dosing can be rounded based on patient weight and available G-CSF vial sizes to best approximate 10µg/kg/d. (e.g. <70kg use 2x 300 = 600 mcg, 70 to 90kg use 300 + 480 = 780 mcg and >90kg use 2 x 480 = 960mcg vials). Continue growth factor daily until apheresis collections are complete.

- Monitor CBC at day + 5, +7, then daily until hematologic recovery.

- Collect apheresis PBSC (see appendix III) daily x 3-4 days beginning on the first day following neutrophil recovery to $\geq$ 700/μl.

- Continue daily collections until a minimum of 2.0 x $10^6$ CD34 cells / kg (target 5.0 x $10^6$ CD34 cells / kg) are collected and cryopreserved. If any collection yields < 0.5 x $10^6$ CD34 cells / kg then re-evaluate the likelihood of collecting the needed minimum of $\geq$ 2.0 x $10^6$ CD34 cells / kg.

- If < 1.2 x $10^6$ CD34 cells / kg are collected in 3 collections; stop apheresis. Wait 2 weeks or until complete hematologic recovery (Hemoglobin $\geq$ 9gm/dl; WBC $\geq$ 2500/μl; neutrophils $\geq$ 1500/μl; platelets $\geq$ 100,000/μl) and recollect. Plerixafor may be added along with G-CSF to improve collections.

- Patients with a final cryopreserved total graft of < 2.0 x $10^6$ CD34 cells / kg are not eligible to proceed under this protocol. Allo-transplantation or non-transplant therapy should be considered

4.1.1 Supportive care during priming cycle
  - Cyclophosphamide will be given as a 2 hour i.v. infusion with vigorous hydration.
  - Mesna will be given in 5 divided doses (totaling 4gm/$m^2$) given pre-cyclophosphamide and 3 hours, 6 hour, 9 hours and 12 hours after cyclophosphamide.
  - Growth factor (G-CSF 10 μg/kg/day rounded to vial size as above) will begin on day 4 and will continue daily until the completion of leukapharesis.
  - All patients will receive allopurinol 300mg/day po beginning prior to each priming cycle and discontinuing on day 7 unless hyperuricemia persists (uric acid > 10 mg/dl).
  - Patients developing fever or other symptoms of infection while neutropenic will be aggressively treated with parenteral broad spectrum antibiotics.

4.2 Transplant admission

4.2.1 After placement of double lumen right atrial catheter for vascular access (if not already in place), begin cytoreductive preparation for transplantation.

4.2.2 High-dose melphalan will be given between 4 and 8 weeks after the initiation of mobilization chemotherapy.

| **Day** | **-2** | **-1** | **0** | **5+ to Engraftment** |
|---|---|---|---|---|
| Melphalan | X | | | |
| PBSC Infusion | | | X | |

| | | | | |
|---|---|---|---|---|
| G-CSF (5 μg/kg/d*) SC or IV until ANC >500 x 3 days | | | | X |

G-CSF dosing can be rounded based on patient weight and available G-CSF vial sizes to best approximate 5μg/kg/d. (e.g. <70kg use 300mcg vial, 70 to 90kg use 480mcg vial and >90kg use 480mcg vials).

4.2.3 Allopurinol: Patients will receive 300 mg/day of allopurinol, starting on Day -3 and ending on Day –1.

4.2.4 Melphalan administration

Patients with GFR >30ml/min

- Dosage: Melphalan will be administered at a dose of 200mg/$m^2$. This will be given in one dose infused on Day –2. Dose will be calculated based on adjusted ideal body weight (AIBW).
- Adjusted Body Weight Formulas:
  Ideal body weight (IBW) is calculated as follows:
  Males IBW = 50 kg + [2.3 kg x (height in inches-60)]
  Females IBW = 45.5 kg + [2.3 kg x (height in inches-60)]
  Adjusted ideal body weight (AIBW) is calculated as follows
  AIBW= IBW + 0.25 x [actual body weight (ABW)- ideal body weight (IBW)]
  For patients whose actual body weight (ABW) is less than ideal, their ABW will be used as the corrected weight.
- Administration:
  High-dose Melphalan is administered via a central venous catheter following reconstitution with the provided sterile diluent. High-dose melphalan should be administered undiluted as a bolus injection or diluted with sodium chloride and infused over 15-20 minutes.
- Maintenance hydration:
  Vigorous maintenance hydration (≥ 1500ml/$m^2$/day) will be administered with high dose melphalan and for 2-4 hours following (day –2 and –1).

  Melphalan dose adjustment for patients with severe renal dysfunction (GFR≤ 30 ml/min)[22,23]
  - Reduce melphalan dose to 140 mg/$m^2$
  - Consider addition of palifermin i.v. 60mcg/kg/day for 3 consecutive days before and after melphalan (total of 6 doses).
    First three doses to be given -6, -5,-4 in clinic
    Last three doses given day 0, + 1, + 2

4.2.5 Peripheral blood stem cell infusion All patients will receive an autologous graft with a minimum cell dose of 2.0 x $10^6$ CD34+ cells/kg.

4.3 G-CSF

Patients will receive ~5μg/kg/d of G-CSF subcutaneously from Day +5 post-transplant until ANC >2500/μl x 2 days or day +28. G-CSF dosing can be rounded based on patient weight and available G-CSF vial sizes to best approximation of 10μg/kg/d (G-CSF dosing can be

rounded based on patient weight and available G-CSF vial sizes to best approximate 5μg/kg/d. (e.g. <70kg use 300mcg vial, 70 to 90kg use 480mcg vial and >90kg use 480 mcg vials).

4.4 Radiation therapy

No radiation therapy is permitted concurrent with administration of melphalan. When palliation of pain from bone lesions or prevention of pathologic fractures is needed or spinal cord compression or nerve root compression is present, if blood count recovery is adequate (ANC >1000/μl, platelets >100,000/μl) radiation may be administered after consultation with a radiation oncologist:

The radiation oncologist will determine dose and duration of radiation to be administered. Radiation to the liver or lungs should be avoided.

In addition to blood count recovery, except for emergent indication (e.g. cord compression), patients must also be recovered from autologous transplantation with resolution of mucositis, resolution of fever, discontinuation of antibiotics and adequate oral hydration and nutrition to receive radiation therapy.

4.5 Administration of zolendronic acid is recommended but not required for all patients with lytic bone disease. Patients will be individually evaluated by their physicians to assess the need and safety for administration of zolendronic acid. Dosing will be zolendronic acid, 4mg I.V. over 30-60 minutes q month. Consider calcium + vitamin D supplements if serum calcium is normal.

## 5.0 MAINTENANCE THERAPY

Maintenance therapy will be administered as clinically indicated using a standard treatment of choice independent of this study.

## 6.0 REQUIRED OBSERVATIONS AND SAE REPORTING

**Targeted days may be altered as clinically appropriate.**

In addition to complete history and physical examination with detailed recording of initial sites and characteristics of disease at diagnosis, previous chemotherapy and radiation as well as evidence of previous response, patients will undergo multi-organ screening to assess their eligibility for initiation into the study treatment protocol.

6.1 Staging

Staging studies to define the extent of disease will include: bilateral bone marrow aspiration and biopsy, x-ray skeletal survey, urine and serum protein electrophoresis, LDH, Beta-2 microglobulin, calcium, creatinine, and CBC.

Staging will be performed: at enrollment to study;; at Day +100, then q 3 months during the first post-transplant year (6 months, 9 months, and 1 year), then at 6 month intervals in the second and third year post-transplant and yearly thereafter.

Restaging skeletal survey should include all previously abnormal bony sites plus representative skull and long bone x-rays of previously uninvolved sites.

6.2 Diagnostic Blood And Bone Marrow Aspiration And Biopsy Studies

All diagnostic blood and bone marrow aspiration and biopsy studies (at study entry, after PBSC collection and pre-transplant, Day +100 and thereafter) shall include the following:

- Unilateral aspirate and bilateral bone marrow biopsies for light microscopic morphologic studies
- Aspirate for immunophenotyping (myeloma panel; Cell Marker Lab 3-5248);

6.3 Prompt Reporting of Events

Toxicity and adverse events will be classified according to NCI's Common Terminology Criteria for Adverse Events V 3.0 (CTCAE). A copy of the CTCAE can be downloaded from the CTEP home page http://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcaev3.pdf

The following categories of events are considered promptly reportable and should be submitted to the IRB via the appropriate forms within **5 working days** of when the researcher receives knowledge of the event:

- Unanticipated death of a locally enrolled subject. A locally enrolled subject means one that is enrolled in in a protocol that is a) approved by the U of M IRB and b)that is directed by an investigator employed by the U of M.
- New or increased risk (For example, publications indicating a new risk, new risk in an investigator brochure, FDA black box warning, new risk identified in a data safety monitoring report, information or change that adversely affects subject safety, or information or change that adversely affects the conduct of the research)
- Adverse events that require a change to the protocol or consent form
- Protocol deviation due to the action or inaction of the investigator or research staff
- Protocol deviation that harmed a subject or placed subject at risk of harm
- Protocol deviation made without prior IRB approval to eliminate an immediate hazard to a subject
- Unauthorized disclosure of confidential information
- Unresolved subject complaint

Additional information and the IRB's Report Form are found at
http://www.research.umn.edu/irb/guidance/ae.html#.VNru7cmwSSw

## 7.0 STUDY ENDPOINTS

7.1 The major clinical endpoint for this treatment trial will be the percent of patients achieving complete response (CR) to the total therapy determined at Day +100, 6 months and 1 year post transplant. The best attained response will be considered. Refer to appendix II for response definitions.

7.2 The second major endpoint will be extended disease-free survival. Extended disease free survival will be defined as percentage of patients surviving more than 36 months without relapse or disease progression.

7.3 Secondary endpoints will include: overall survival, transplant-related mortality, incidence of relapse and disease progression, hematologic recovery, time to progression and relapse, time to attainment of CR and CR+PR, duration of maintenance treatment, drop-out rate from maintenance treatment, incidence of toxicities and incidence of infections.

## 8.0 TOXICITIES AND COMPLICATIONS

8.1 Cyclophosphamide

- Hemorrhagic cystitis may occur following the use of cyclophosphamide. Aggressive fluid replacement (2-3,000 ml/$m^2$/24 hours) is recommended along with frequent voiding (every 1-2 hours) and Mesna. Because of the antidiuretic effect of cyclophosphamide, furosemide may be required to maintain urine output in face of this aggressive fluid support. Careful monitoring of electrolytes, intravascular volume status and body weight are required during the 48 hours following the treatment with cyclophosphamide.

- Oral/gastrointestinal mucositis may develop.

- Cardiomyopathy: Cyclophosphamide can cause fatal cardiac necrosis with clinical irreversible heart failure. Non-specific EKG changes are not infrequent and reduction in EKG voltage may be observed. In patients previously treated with anthracyclines or with mediastinal irradiation, cyclophosphamide (with or without irradiation) may induce pericarditis.

- Myelosuppression: even with the use of hematopoietic growth factors, significant neutropenia is expected, though it will likely be of brief duration. Neutropenic infections and/or need for transfusions of red cells and/or platelets may result.

- Nausea and vomiting are frequent: Aggressive anti-emetic therapy including ondansetron may be helpful in minimizing this problem.

- Alopecia follows these doses of cyclophosphamide frequently. It is usually reversible but changes in hair color or texture after regrowth are sometimes noted.

- Skin rash may develop, but is infrequent.

- Sterility. Permanent sterility may occur with cyclophosphamide.

8.2 Hematopoietic growth factor: G-CSF

- G-CSF may be associated with development of fevers, chills, skin rash, polyserositis, muscle aches, malaise and/or headache. It has also been reported to cause bone aches or pain in a minority of patients.

- Some myeloma cells may respond in vitro with proliferation after exposure to G-CSF. No clinical evidence of accelerated myeloma growth using this hematopoietic growth factor has been reported.

8.3 Peripheral stem cell collection

- Large bore double lumen intravenous Hickman-type catheters are required for the venous access necessary to perform leukopheresis and peripheral blood stem cell collections. The four-six hour collection procedures are occasionally associated with hypotension and/or transfusion reactions. Thrombocytopenia might develop transiently following the leukopheresis and, if necessary, autologous and/or irradiated Blood Bank platelet concentrates will be reinfused.

8.4 High-dose Melphalan

- Myelosuppression: even with the use of hematopoietic growth factors, significant neutropenia is expected. Neutropenic infections and/or need for transfusions of red cells and/or platelets may result.

- Stomatitis, esophagitis and severe diarrhea are common with high dose melphalan: management with i.v. narcotics and potentially i.v. alimentation may be needed.

- Other less common toxicities reported include pulmonary fibrosis and interstitial pneumonitis, skin hypersensitivity, vasculitis, alopecia, hemolytic anemia and allergic reaction.

## 9.0 EXPERIMENTAL DESIGN AND STATISTICAL CONSIDERATIONS

9.1 Primary Objective

The primary objective is to induce a complete remission for treated patients. A total of 250 patients will be enrolled over a period of 10 years.

9.2 Stopping Boundaries

There will not be any stopping boundaries as the rate of adverse effects from the conditioning regimen is well documented and the regimen is a standard of care. Toxicities from the

maintenance therapy, if severe, may result in stopping the medications but would not be a reason for stopping the trial.

## 9.3 Statistical Analysis

### 9.3.1 Final Analysis

The primary outcome variable is (P), the proportion of patients achieving a CR. This outcome will be evaluated at 100 days, 6 months and 1-year post transplant. The evaluation at 1-year post transplant will be the primary time-point of interest since we are interested in the effect of the conditioning in conjunction with the maintenance therapy. Assuming 50% of patients reach CR, a sample size of 250 patients will produce a two-sided confidence interval with a width equal to 0.127 (0.436-0.564) (newcombe, R.G., 1998).

Patients who die too early for evaluation will be considered non-evaluable for response and the cause of death noted.

A second major outcome will be disease-free survival. Disease-free survival will be estimated by the Kaplan-Meier method.

Secondary outcomes include survival, non-relapse mortality, incidence of relapse and disease progression, time to progression and relapse, time to attainment of CR and CR+PR, duration of maintenance treatment, drop-out rate from maintenance treatment, hematologic recovery, and the incidence of toxicities and infections. Survival will be estimated by the Kaplan-Meier method. Non-relapse mortality, incidence of relapse and disease progression and hematologic recovery will be estimated by cumulative incidence treating non-event deaths as a competing risk.

### 9.3.2 Interim Analysis

Due to the long duration of the study, an interim analysis will be carried out at 2-3 years after the initiation of the study. All primary and secondary outcomes will be estimated at this time as specified in 9.3.1.

## 9.4 Data Collection and Safety Monitoring Plan

Standard pre- and post-transplant data will be recorded on the BMT research database. Patients will be followed for hematologic recovery, infection, relapse, death and length of hospitalization according to standard procedures.

The protocol chair (PI) will be responsible for the primary outcome assessments.

The BSG will immediately enter reportable SAE's on the "Toxicity" table of the database. Annual summaries will be generated by the BSG to help the PI monitor the protocol for adverse events as well as efficacy.

## 10.0 ETHICAL AND REGULATORY CONSIDERATIONS

10.1 Good Clinical Practice

The study will be conducted in accordance with the appropriate regulatory requirement(s). Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

10.2 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted at sites where IRB approval has been obtained. The protocol, informed consent, written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the investigator.

10.3 Informed Consent

All potential study participants will be given a copy of the IRB-approved Informed Consent to review. The investigator or designee will explain all aspects of the study in lay language and answer all questions regarding the study. If the participant decides to participate in the study, he/she will be asked to sign and date the Informed Consent document. Patients who refuse to participate or who withdraw from the study will be treated without prejudice.

## 11.0 DATA AND SAFETY MONITORING PLAN AND RECORD RETENTION

11.1 Data and Safety Monitoring Plan (DSMP)

The study's Data and Safety Monitoring Plan will be in compliance with the University of Minnesota Masonic Cancer Center's Data & Safety Monitoring Plan (DSMP), which can be accessed at http://z.umn.edu/dmsp .

For the purposes of data and safety monitoring, this study is classified as moderate risk. Therefore the following requirements will be fulfilled:

- The PI will complete and submit a quarterly Trial Progress Report to the Masonic Cancer Center Data and Safety Monitoring Council (DSMC) with the understanding the Cancer Protocol Review Committee (CPRC) may require more frequent reporting.
- The PI will comply with monitoring of the project by the Masonic Cancer Center monitoring services.
- The PI will oversee the submission of all reportable adverse events per the definition of reportable in section 6.3 to the Masonic Cancer Center's SAE Coordinator and the University of Minnesota IRB.

In addition, at the time of the continuing review with the University of Minnesota IRB, a copy of the report with any attachments will be submitted to the Cancer Protocol Review Committee (CPRC).

11.2 Monitoring

The investigator will permit study-related monitoring, audits, and inspections by the IRB, government regulatory bodies, and University of Minnesota compliance groups. The investigator will make available all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data, etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.) will be available for trial related monitoring, audits, or regulatory inspections.

11.3 Record Retention

The investigator will retain study records including source data, copies of case report form, consent forms, HIPAA authorizations, and all study correspondence in a secured facility for at 6 years after the study file is closed with the IRB.

In addition, the Clinical Trials Office (CTO) will keep a master log of all patients participating in the study with sufficient information to allow retrieval of the medical records for that patient.

Please contact the CTO before destroying any study related records.

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# Appendix I –

## KARNOFSKY AND ECOG PERFORMANCE STATUS

| Karnofsky Performance Status | | Eastern Cooperative Group Performance Status (ECOG) | |
|---|---|---|---|
| 100 | Normal, no complaints | 0 | Fully active, able to carry on all pre-disease performance without restriction |
| 90 | Able to carry on normal activities. Minor signs or symptoms of disease | 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work |
| 80 | Normal activity with effort | 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work |
| 70 | Care for self. Unable to carry on normal activity or to do active work | 2 | Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours |
| 60 | Requires occasional assistance, but able to care for most of his needs | 2 | Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours |
| 50 | Requires considerable assistance and frequent medical care | 3 | Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours |
| 40 | Disabled. Requires special care and assistance | 3 | Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours |
| 30 | Severely disabled. Hospitalization indicated though death nonimminent | 4 | Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair |
| 20 | Very sick. Hospitalization necessary. Active supportive treatment necessary | 4 | Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair |
| 10 | Moribund | 4 | Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair |
| 0 | Dead | 5 | Dead |

As published in Am J Clin. Oncol.: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

## Appendix II – Myeloma Response Definitions

(Using International Uniform Response Criteria)

**Stringent Complete Response (sCR)**

sCR requires, in addition to CR (defined below), all of the following:

- Normal free light chain ratio (FLC).
- Absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence[a].

**Complete Response (CR)**

CR requires *all* of the following:

- Absence of the original monoclonal paraprotein in serum and urine by routineelectrophoresis and by immunofixation. The presence of new monoclonal bandsconsistent with oligoclonal immune reconstitution does not exclude CR.
- Less than 5% plasma cells in a bone marrow aspirate and also on trephine bone biopsy, if biopsy is performed.
- No increase in size or number of lytic bone lesions on radiological investigations (development of a compression fracture does not exclude CR)*.
- Disappearance of soft tissue plasmacytomas.

**If not clinically indicated, radiographs are not required to document CR.*

Patients in whom some, but not all, the criteria for CR are fulfilled are classified as partial responses (see below), providing the remaining criteria satisfy the requirements for partial response. This includes patients in whom routine electrophoresis is negative but in whom immunofixation has not been performed.

**Very Good Partial Remission (VGPR)**

VGPR requires, in addition to PR (defined below), all of the following:

- Serum or urine paraprotein detectable by immunofixation but not on electrophoresis.

OR

- Greater than or equal to 90% reduction in serum paraprotein plus urine paraprotein <100 mg/24hrs.

**Partial Response (PR)**

PR requires one of the following:

- Greater than or equal to 50% reduction in the level of the serum monoclonal paraprotein and/or reduction in 24 hour urinary monoclonal paraprotein either by greater than or equal to 90% or to <200 mg/24 hours in light chain disease.
- If the only measurable non-bone marrow parameter is FLC, greater than or equal to 50% reduction in the difference between involved and uninvolved FLC levels or a 50% decrease in level of involved FLC with 50% decrease in ratio,
- If the bone marrow is the only measurable parameter, greater than or equal to 50% reduction in bone marrow plasma cells given that the baseline count was greater or equal to 30%,.
- Greater than or equal to 50% reduction in the size of soft tissue plasmacytomas (by radiography or clinical examination).

**Stable Disease (SD)**
Patients who do not meet criteria for sCR, CR, VGPR, partial response or progressive disease are considered to have stable disease (SD).

**Relapse or Progressive Disease (PD)**
**Disease Relapse**
Relapse from CR or sCR requires one or more of the following:

- Reappearance of serum or urine paraprotein on routine electrophoresis. Paraproteins detected only by immunofixation requires two separate assessments to define relapse.
- Greater than or equal to 5% plasma cells in a bone marrow aspirate or on trephine bone biopsy.
- Development of new lytic bone lesions or soft tissue plasmacytomas or definite increase in the size of residual bone lesions. Development of a compression fracture does not exclude continued response and may not indicate progression.
- Development of hypercalcemia (corrected serum Ca >11.5 mg/dL or >2.8 mmol/L) not attributable to any other cause.

**Progressive Disease (PD)**
For patients not in CR or sCR, progressive disease requires one or more of the following:

- >25% increase in the level of the serum monoclonal paraprotein, which must also be an absolute increase of at least 0.5 g/dL.
- >25% increase in 24-hour urine protein electrophoresis, which must also be an absolute increase of at least 200 mg/24 hours.
- Absolute increase in the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dl), only in patients without measurable paraprotein in the serum and urine.
- >25% increase in plasma cells in a bone marrow aspirate or on trephine biopsy, which must also be an absolute increase of at least 10%.
- Definite increase in the size of existing bone lesions or soft tissue plasmacytomas.

## Appendix III: Cell Collection, Storage And Use/ Vascular Access For Apheresis

**Targeted days may be altered as clinically appropriate**.

Peripheral blood stem cells will be collected using available apheresis machines. Currently at the University of Minnesota, FUMC, the Fenwal CS3000 is available and will be used. A standard technique using a modification of program one, running at 1400 rpm, will be used. Procedures will be performed using **Quinton/Davol** catheters for apheresis collection. Peripheral blood mononuclear cell collections will be performed daily for 5-6 hours on each day. A minimum target of 5 x $10^6$ and of 2.0 x $10^6$ CD34+ cells/kg generally obtained in 3-4 apheresis collections will be required to proceed. If < 2 x $10^6$ /kg CD34 cells are collected (or <1.0 x $10^6$/kg in the first two apheresis runs) then the patient will be considered a PBSC collection failure and transplant cannot proceed without additional PBSC collections. If additional cell collections are required, then they will be collected following at least 2 weeks rest; off cytokines with complete hematologic recovery (Absolute neutrophil count (ANC) >2500/µl; platelets > 100,000/µl). Then the G-CSF (10 mcg/kg/d) will be given for 5-8 days with apheresis collections on days 6-8 as needed. No additional chemotherapy will be given.

**All collected cryopreserved cells are to be infused on day 0.**

Cells will be prepared for cryopreservation in the Cell Processing Laboratory. Peripheral blood stem cells, if over-contaminated with red cells (greater than 15% hematocrit), will be spun to produce a buffy coat. If the hematocrit is less than 15% this will not be necessary. The cells will be resuspended in protein containing media at a concentration of ≤ 200 x $10^6$ nucleated cells/ml. An equal volume of 20% dimethylsulfoxide (DMSO) in protein containing media will be added for final concentration of ≤ 100 x $10^6$ nucleated cells/ml and 10% DMSO. The cell concentrate will then be frozen at a controlled rate in a programmable controlled rate freezer (1°/minute through -60°C and 3°/minute through -90°C). The frozen cell concentrates will be stored in the liquid phase of liquid nitrogen. Quality control including careful measurement of red cell concentration, volumes, white cell numbers, and CD34+ cell content will be performed.