UNIVERSITY OF MINNESOTA BONE MARROW TRANSPLANTATION PROGRAM

MT2005-21

AUTOLOGOUS PERIPHERAL BLOOD STEM CELL TRANSPLANT FOR GERM CELL TUMORS

VERSION 4

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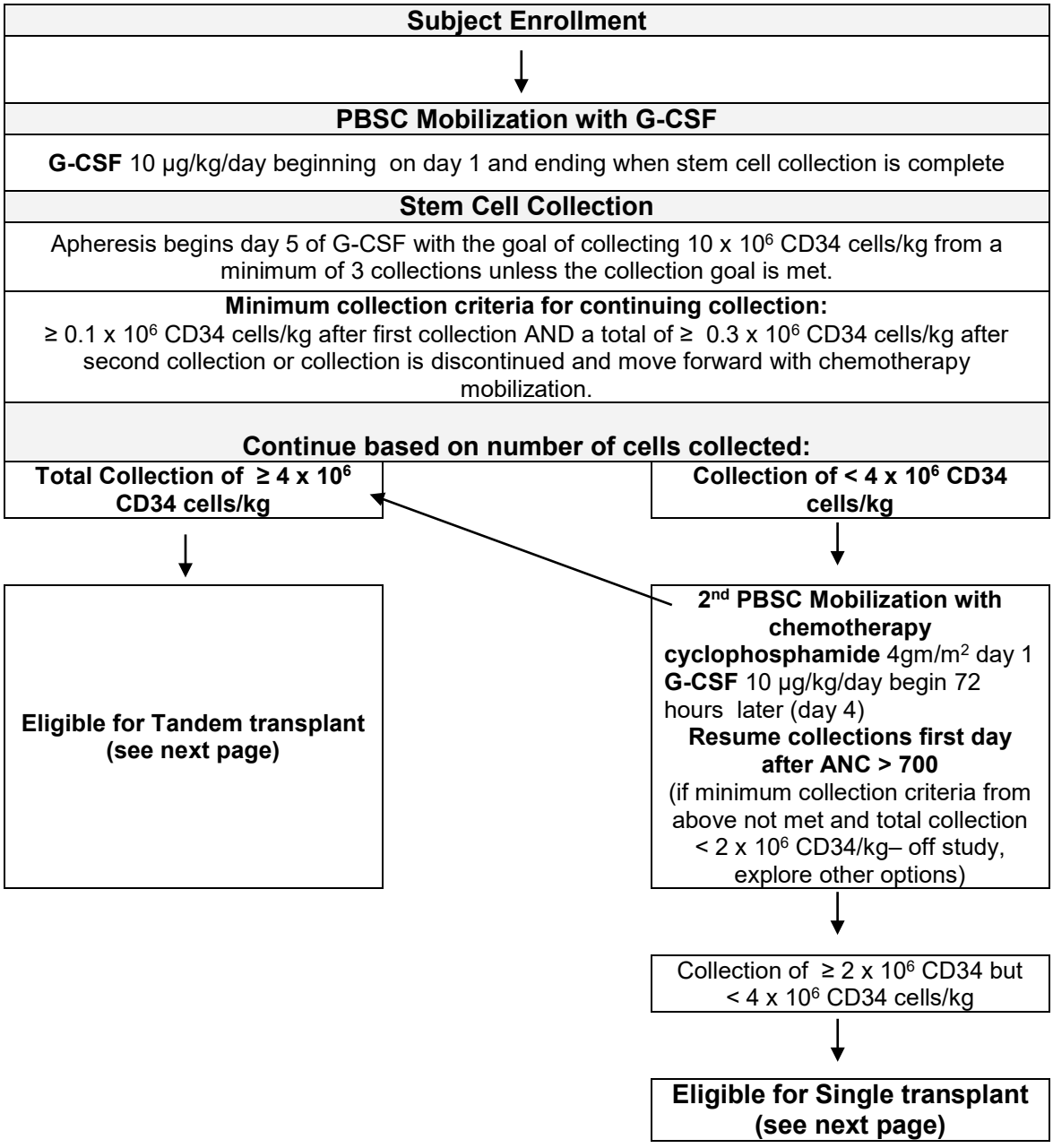
Revision History

Date	Revision details	Consent change/ version date
1-29-07	The goal collection is 10 X 10^6 $CD34^+$ cells/kg instead of 6 X 10^6 $CD34^+$ cells/kg to reflect a goal of 5 x10^6 $CD34^+$ cells/kg for infusion for each transplant.	
3-13-2008	Clarified exclusion criteria to state that patients with progressive disease will not be eligible for a second transplant, added RECIST criteria (as appendix IV), fixed typo in section 5.5 Removed Dr. Nasfat Shehadeh from protocol team	
6-15-09	Dr. Brian McClune takes over as PI; Dr Tomblyn removed from study	
9/9/2009	Typo correction in schema	
9/27/2010	Typo correction in schema	
1/10/11	Error correction in peds fluid hydration rate	
09/12/2018	Dr Brunstein is PI	
07/12/2019	Dr. El Jurdi takes over as Principal Investigator	Y

SCHEMA

MOBILIZATION AND STEM CELL COLLECTION



TRANSPLANT

Admit within 2 weeks of completing Cell Collection

Tandem Transplant (Transplant 1 and 2) | **Single Transplant (Transplant 1 only)**

Transplant 1 (all subjects)

Day	Treatment
-8	Admission for IV fluids
-7	Paclitaxel
-6	Ifosfamide + Mesna
-5	Ifosfamide + Mesna
-4	Ifosfamide + Mesna
-3	Rest
-2	Rest
-1	Rest
0	Cell re-infusion (transplant)
+5	G-CSF 5 µg/kg/day until ANC ≥ 1500/UL for 3 consecutive days

Assess for Transplant 2
admission for transplant must be no earlier than day +30 and no later than day +90 (goal day +40- +60)
If not eligible for transplant 2 → Standard transplant follow-up (see appendix IIIA)

If eligible, admit for transplant 2

Transplant 2 (if eligible)

Day	Treatment
-7	Admit, begin hydration
-6	carboplatin, thiotepa, etoposide
-5	carboplatin, thiotepa, etoposide
-4	carboplatin, thiotepa, etoposide
-3	etoposide
-2	rest
-1	rest
0	Cell re-infusion (transplant)
+5	G-CSF 5 µg/kg/day until ANC ≥ 1500/UL for 3 consecutive days

Standard transplant follow-up (see appendix IIIB)

1.0 Background And Rationale

1.1 BACKGROUND

Germ cell tumors (GCT) are highly sensitive to chemotherapy such that even with metastatic disease at diagnosis, many patients can be cured—greater than 90% 5-year overall survival—at the time of diagnosis[1]. The International Germ Cell Consensus Classification divides patients based on risk factors into good, intermediate and poor prognostic categories to better estimate outcomes [Appendix I][2]. Many patients who fall into the poor risk category or other patients who relapse are successfully salvaged with high dose chemotherapy and autologous stem cell transplant (AuSCT)[3-6].

Beyer and colleagues analyzed 310 patients at four institutions to determine prognostic factors in patients with relapsed GCT treated with AuSCT[7]. Four factors were found to be important in multivariate analysis (Beyer Index):

- progressive disease after salvage therapy immediately prior to transplant
- absolute cisplatin refractory disease (defined as progressive increase in serum markers despite on-going cisplatin chemotherapy) or cisplatin refractory disease (defined as disease progression within 4 weeks of a the last cycle of chemotherapy)
- an hCG level of > 1000 IU/L
- primary mediastinal non-seminomatous GCT

Patients with more than 2 of these factors were considered poor risk with a 2 year relapse free survival of only 5% versus 51% for patients with no risk factors and 27% in patients with 1 or 2 risk factors.

There are other diseases, such as myeloma, in which sequential high dose chemotherapy and AuSCT have demonstrated improved overall and disease free survival[8]. Prior investigations in GCT suggest that a subset of high risk or relapsed patients may be cured with sequential cycles of high dose chemotherapy and AuSCT[4,9]. Interestingly, in the initial prognostic study by Beyer, only 20% of patients were treated with two transplants. An initial pilot study from Margolin et al, demonstrated feasibility of tandem high-dose chemotherapy with AuSCT in a cohort of patients with either high-risk primary disease in partial response or platinum-sensitive relapse[9]. Both conditioning cycles consisted of ifosfamide, carboplatin, and etoposide (ICE). Treatment related mortality was zero and at almost 4 years, 9 of 20 patients enrolled were alive and disease-free. Other studies have looked at sequential therapy with regimens including paclitaxel, a drug found effective in cisplatin-refractory patients[10]. A recent study utilized paclitaxel in both conditioning regimens in 33 patients[11]. At a median follow-up of 5 years, 36% of patients were

alive without disease although only 2 (18%) patients with a Beyer index of ≥ 2 remained progression-free after therapy. Table 1 gives a summary of several studies investigating AuSCT for GCT.

1.2 RATIONALE

The use of either non-cross resistant therapy or more than two high dose therapy cycles are areas of interest[4,10]. In this study, we propose to use tandem transplant with non-cross resistant conditioning regimens to further study these issues. Pre clinical and clinical studies have found that taxanes can salvage patients with cisplatin-refractory GCT[10-14]. As documented in Table 1, most prior studies have not used non-cross resistant conditioning regimens for AuSCT but rather identical conditioning for both transplants. We propose that patients with high-risk or relapsed disease may benefit from using chemotherapeutic agents that have differing mechanisms of action and differing resistance patterns as high dose therapy. This would permit tumor kill prior to development of further resistance.

Mobilization of sufficient numbers of peripheral blood stem cells may not occur in all patients. For those patients collecting ≥ 2 x 10^6 $CD34^+$ cells/kg but < 4 x 10^6 $CD34^+$ cells/kg, only a single transplant can safely be performed. However, it would be inappropriate to deny them AuSCT which is a demonstrated salvage regimen with potential for cure. This protocol accounts for this possibility by providing a treatment option for patients with insufficient PBSC collection for tandem transplantation. The conditioning regimen for the single transplant is identical to the conditioning regimen of Transplant 1 for planned tandem patients.

Table 1

Author	Study Type	Treatment	Patients	N	Response	EFS	OS
Vaena[15]	Retrospective	Carbo + VP16 conditioning; tandem AuSCT if possible	Relapsed, cisplatinum refractory	80 (56 received x2 AuSCT)	45%	32% (2y)	40% (2y)
Rick[16]	Phase II	TIP x3 then Carbo+VP16+TT conditioning	Relapsed disease	80 (62 SCT)	78% (of patients transplanted)	25% (3y)	30% (3y)
Motzer[10]	Phase I/II	Paclitaxel + Ifos x 2 then Carbo + VP16 conditioning	Relapsed cisplatinum refractory and poor prognostic features	37	62%	49% (31 months)	54% (31 months)
Motzer[17]	Phase II	Carbo + VP16 + Cy; tandem AuSCT if possible	Relapsed/refractory disease	58 (27 received x2 AuSCT)	40% CR	21% (2y)	31% (2y)
Bhatia[3]	Retrospective	Carbo + VP16 x2	Relapsed/refractory disease	65 (58 received x2 AuSCT)	63% CR	57% (3y)	68% (3y)
Nichols[6]	Phase II (multicenter)	Carbo + VP16; x2 if possible	Relapsed or refractory disease	38 (22 received x2 AuSCT)	45% (24% CR)	13% (1y)	35% (1y)
Mandanas[5]	Retrospective	Cy + Carbo + VP16 (68% of patients)	Relapsed or refractory	21 (1 received x2 AuSCT)	79%	52% (3y)	52% (3y)
Lotz[4]	Phase II (multicenter)	Epi + Paclitaxel x2 then TT +CY conditiong for SCT1 then ICE conditioning for SCT 2 and 3	Relapsed, poor prognosis disease	45 (7 received x2 SCT, 22 x3 SCT)	38%	24% (3y)	24% (3y)
Rosti[18]	Retrospective	Carbo + VP16 (19); ICE (30); Carbo + VP16 + CY (35)	Relapsed disease	84 (19 received x2 SCT, 1 x 3 SCT)	45% CR	30% (5y)	33% (5y)
Margolin[9]	Phase I/II	ICE conditioning; tandem AuSCT	Poor prognosis, chemotherapy sensitive disease	20 (18 received x2 AuSCT)	60%	45% (3y)	45% (3y)
Margolin[11]	Phase I/II	Paclitaxel + Carbo + VP16 (SCT1); Paclitaxel + Carbo + Ifosfamide (SCT2)	Relapsed or refractory GCT	33 (2 received no SCT; 19 received x2 AuSCT)	Not reported	36% (5y)	42% (5y)

Carbo = carboplatinum, VP16 = etoposide, TT = thiotepa, Cy = cyclophosphamide, Epi = epirubicin, ICE = Ifosfamide + Carboplatinum + Etoposide
EFS = Event-free survival, OS = overall survival, Response = CR + PR unless otherwise stated

2.0 Objectives

End organ toxicities such as myelosuppression often dictate the maximal doses of chemotherapy that can be administered safely. Autologous peripheral blood stem cell transplant (AuSCT) after high-dose chemotherapy circumvents this marrow toxicity allowing for dose intensification. This has been demonstrated to be useful in the salvage setting for patients with relapsed germ cell tumor (GCT)[3-6] The use of non-cross resistant chemotherapy regimens should increase the overall and disease-free survival in patients with high risk or relapsed GCT.

2.1 Primary Objective

To determine overall survival for patients with GCT treated with tandem AuSCT with non-cross-resistant conditioning regimens.

2.2 Secondary Objectives

- 2.2.1 To determine disease-free survival for patients with GCT treated with tandem AuSCT with non-cross-resistant conditioning regimens
- 2.2.2 Evaluate toxicity of tandem AuSCT
- 2.2.3 Evaluate time to engraftment of neutrophils and platelets for each transplant
- 2.2.4 Determine numbers of patients unable to adequately mobilize sufficient peripheral blood stem cells (PBSC) for tandem transplant
- 2.2.5 Identify prognostic factors of those patients unlikely to mobilize sufficient PBSC for tandem transplant
- 2.2.6 Compare outcomes of overall and disease free survival for patients undergoing single versus tandem transplant due to biologic randomization

3 Eligibility Criteria

3.1 **Diagnosis:** Poor Prognosis Non-Seminomas Germ Cell Tumor in ≥ PR1/CR1 **or** Good or Intermediate Prognosis Seminomas and Non-Seminomas Germ Cell Tumor in ≥ PR1 or ≥ CR2 as defined by the International Germ Cell Cancer Consensus Classification (appendix I) Patients with increasing tumor markers only (i.e. no imaging evidence of progressive disease) are eligible for transplant.

3.2 **Age:** ≥ 10 years and < 70 years of age.

3.2 **Performance status:** Karnofsky ≥ 80% (subjects ≥ 16 years of age) Lansky ≥ 80% for subject 10 – 15 years of age [Appendix II]

3.3 **Life expectancy:** Greater than 8 weeks.

3.4 Patients must have normal organ function as defined below:

3.4.1 Hematologic:
Hemoglobin > 8 gm/dL without transfusion and off erythropoietin for 14 days or Aranesp for 21 days
WBC > 2.5 x 10^9/L with an ANC > 1.5 x 10^9/L and off G-CSF or GM-CSF for 10 days or Neulasta for 21 days
Platelets > 100 x 10^9/L without transfusion and/or a bone marrow cellularity of ≥ 20%

3.4.2 Renal: Creatinine ≤ 2.0 mg/dl or creatinine clearance > 50 ml/min.

3.4.3 Hepatic: Total bilirubin ≤ 2.0 mg/dl, AST and alkaline phosphatase < 5 x upper limit of normal. No history of severe prior or ongoing chronic liver disease.

3.4.4 Cardiac: Patients must be free of symptoms of uncontrolled cardiac disease including unstable angina, decompensated congestive heart failure, or arrhythmia. LVEF ≥45% by MUGA/ECHO

3.4.5 Pulmonary: Patients must have no significant obstructive airways disease (FEV_1 must be ≥ 50% of predicted) and must have acceptable diffusion capacity (corrected DLCO > 50% of predicted).

3.5 Patients with a history of CNS tumor involvement are eligible if they have completed treatment for CNS disease (radiotherapy or surgery or chemotherapy), have recovered from or stabilization of the side effects associated with the therapy and have no evidence of progressive CNS disease at the time of enrollment

3.6 Patients with serious uncontrolled infections will not be eligible.

3.7 Male and female patients of reproductive potential must use an approved contraceptive method if appropriate (for example, intrauterine device [IUD], birth control pills, or barrier device) during and for the duration of study participation. The drugs used in this study are pregnancy category D – clear evidence of risk in pregnancy. Pregnant and breast feeding women will not be eligible.

3.8 Voluntary written informed consent before performance of any study-related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the subject at any time without prejudice to future medical care.

3.9 Additional Eligibility prior to Transplant Two

3.9.1 Total Collection of $\geq 4 \times 10^6$ CD34 cells/kg prior to transplant one

3.9.2 Transplant able to occur between day +30 and day +90 from transplant one

3.9.3 Recovery of blood counts as demonstrated by:
WBC > 2.5×10^9/L with an ANC > 1.5×10^9/L and off G-CSF for 3 days
Platelets > 50×10^9/L without transfusion in the prior 7 days

3.9.4 Renal: Creatinine ≤ 2.0 mg/dl or creatinine clearance > 50 ml/min

3.9.5 Hepatic: Total bilirubin ≤ 2.0 mg/dl, AST and alkaline phosphatase < 5 x upper limit of normal

3.9.6 Infection: Patients with serious uncontrolled infections at the time of planned transplant will be excluded

3.9.7 Patients with progressive disease by RECIST criteria (Appendix IV) by imaging techniques are not eligible to proceed to the second transplant. Tumor marker increase alone is not sufficient to diagnose disease progression.

4 Subject Registration

Informed consent must be signed prior to the performance of any study related procedures or assessments.

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. No exemptions or waivers will be granted for patients who do not meet the eligibility criteria.

4.1 Registration with the University of Minnesota Clinical Trials Office (CTO)

To register a patient to this study, complete the Subject Registration Form and study specific eligibility checklist and fax it to the Clinical Trials Office Registrar at (612) 625-3624. Confirmation of registration with the study assigned patient ID number will be returned by email and/or fax within 1 working day.

4.2 Patients who are registered and do not begin study treatment

If a patient is registered to the study, and is later found not able to begin the planned study treatment, for whatever reason, the patient will be removed from study and treated at the physician's discretion. The CTO Registrar will be notified of the patient's non-treatment status. Study data will be collected until the time the patient is off study. The reason for removal from study will be clearly indicated on the case report forms. The registration number cannot be reassigned.

5 TREATMENT PLAN

5.1 G-CSF Mobilization of Peripheral Blood Hematopoietic Stem Cells

Patients will be treated with Granulocyte colony stimulating factor (G-CSF) 10µg/kg/day (rounded to the nearest vial size) beginning 5 days before the first planned apheresis and continuing until the last aphereresis.

Begin peripheral blood stem cell collection per section 5.2 on day 5 of G-CSF mobilization.

5.2 Peripheral blood stem cell collection

Daily peripheral blood stem cell collection will continue for a minimum of 3 days unless the goal of 10 x 10^6 $CD34^+$/kg is reached earlier.

Minimum collection criteria for continuing collection:
The first collection must yield ≥ 0.1 x 10^6 CD34 cells/kg
After the second collection a total of ≥ 0.3 x 10^6 CD34 cells/kg must have been collected. If either of these conditions is not met, apheresis is discontinued and the subject will begin Chemotherapy Mobilization per section 5.3.

Total cell collection of ≥ 4 x 10^6 $CD34^+$ cells/kg
A total cell collection of ≥ 4 x 10^6 $CD34^+$ cells/kg is considered sufficient for the tandem transplant (Transplant 1 plus Transplant 2). The collected PBSC will be cryopreserved such that approximately 50% of the leukapheresed product can be thawed and infused for each transplant. Patient will proceed to transplant 1 per section 5.4.

Total cell collection of ≥ 2 x 10^6 $CD34^+$ cells/kg but < 4 x 10^6 $CD34^+$ cells/kg
If patients cannot be adequately collected with GCSF mobilization (< 4 x 10^6 $CD34^+$ cells/kg) Chemotherapy Mobilization will be done per section 5.3.

5.3 Chemotherapy Mobilization and cell collection (for patients with a total cell collection of < 4 x 10^6 $CD34^+$ cells/kg)

Chemotherapy mobilization:

Mesna 800mg/m^2 IV

Cyclophosphamide 4gm/m^2 intravenously (IV) over 2 hours

Mesna 800mg/m^2 IV 3 hours, 6 hours, 9 hours, and 12 hours following the cyclophosphamide

G-CSF 10µg/kg/day (rounded to nearest vial size) beginning 72 hours after completion of cyclophosphamide (day 4) and continuing until leukapheresis is completed

The dose of cyclophosphamide will be calculated using actual body weight unless the patient is ≥120% of Ideal Body Weight (IBW) in which case, the Cyclophosphamide dose will be based on Adjusted Ideal Body Weight (AIBW).

IBW_{men} = 50kg + 2.3kg (inches of height over 60in)

IBW_{women} = 45kg + 2.3kg (inches of height over 60in)

AIBW = IBW + 1/3(ABW - IBW)

Standard Cyclophosphamide hydration orders will be used.

Monitor CBC daily starting on day 4. Leukapheresis will start on the first day following an absolute neutrophils count (ANC) ≥ 700/µL.

Minimum collection criteria for continuing collection:

The first collection must yield ≥ 0.1 x 10^6 CD34 cells/kg

After the second collection a total of ≥ 0.3 x 10^6 CD34 cells/kg must have been collected.

If patient has received chemotherapy mobilization and the minimum criteria cannot be met, the cell collection should be stopped. If the patient has collected > 2 x 10^6 CD34 cells/kg with the combined aphereses, the patient is eligible for a single transplant. If the total collections are < 2 x 10^6 CD34 cells/kg, the patient is removed from study, and other treatment options discussed.

5.4 Transplant One

Admit for transplant within two weeks of completing cell collection.

Day	Drug	Administration
-8 (Admit)		Admit to start premedications per section 5.4.1 and hydration per section 5.4.2
- 7	Paclitaxel	225 mg/m^2 IV over 3 hours starting at 0900 • Dilute in 5% dextrose or 0.9% saline to a concentration of 0.3 – 1.2 mg/mL • Administer using a 0.22µM filter and polyethylene-lined administration set
-6, -5, -4	Ifosfamide Mesna	2500mg/m^2/day continuous infusion IV starting at 0900 2500mg/m^2/day continuous infusion IV starting at 0900 • See section 5.4.3 for ifosfamide dose calculation • Combine mesna and ifosfamide in 1L D_5W
0		PBSC infusion
+5 until ANC ≥ 1500/µL for 3 consecutive days	G-CSF	5µg/kg/day (round to nearest vial size) SC or IV. May be restarted if ANC falls below 1000/µL

5.4.1 Premedication for Paclitaxel administration

- Dexamethasone 20 mg PO at 12 hours and 6 hours before administration. For pediatric patients, 5 mg/m^2 q 12 hrs

- Diphenhydramine 50mg IV 30 minutes before administration. For pediatric patients, 1 mg/kg q 6 hrs

- Ranitidine 50mg IV 30 minutes before administration. For pediatric patients, 1-2 mg/kg/day divided q 8 hrs

5.4.2 Hydration

Normal Saline at 100mL/hour starting 10 hours before paclitaxel administration. For pediatric patients, slower infusion rates may be used with a goal infusion of 1500 ml/m^2 over 24 hours

At the completion of paclitaxel infusion, hydration should be increased to 2000 – 3000 mL/m^2/day until 24 hours after completion of ifosfamide.

Adequate diuretics should be given and patients urged to urinate every 1 - 2 hours to ensure urinary output of at least 200 mL every 2 hours and to maintain appropriate fluid balance. Patients should

be weighed BID during ifosfamide administrations to aid in managing fluid balance.

5.4.3 Dosing of Ifosfamide

Dosing of ifosfamide will be per actual body weight unless the patient is ≥120% of Ideal Body Weight (IBW) in which case, the Ifosfamide dose will be based on Adjusted Ideal Body Weight (AIBW)

IBW_{men} = 50 kg + 2.3kg (inches of height over 60in)
IBW_{women} = 45 kg + 2.3kg (inches of height over 60in)

AIBW = IBW + 1/3(ABW - IBW)

For patients qualifying to have only a single transplant (due to a collection of < 4 x 10^6 $CD34^+$ cells/kg) follow-up will be per appendix IIIA.

For patients qualifying to have a tandem transplant (transplant one and transplant two), study participation will continue per section 5.5.

5.5 Transplant Two

Admission for transplant two will be no earlier than day 30 from first transplant and no later than day 90. Goal for admission is day 40-60. See section 3.9 for additional eligibility criteria for continuing with transplant 2.

Day	Drug	Administration
-7 (Admit)		Admit to start hydration per section 5.5.1
-6, -5, -4	Carboplatin	500mg/m^2/day IV over 60 minutes
-6, -5, -4	Thiotepa	150mg/m^2/day IV over 30 minutes; see section 5.5.2 for skin care
-6, -5, -4, -3	Etoposide	600mg/m^2/day IV over 60 minutes
0		PBSC infusion
+5 until ANC ≥ 1500/µL for 3 consecutive days	G-CSF	5µg/kg/day (round to nearest vial size) SC or IV. May be restarted if ANC falls below 1000/µL

5.5.1 Hydration

0.45% saline at 100mL/hour starting 10 hours before chemotherapy administration.
For pediatric patients, slower infusion rates may be used with a goal infusion of 1500ml/m^2 over 24 hours

5.5.2 Thiotepa

Because Thiotepa can be excreted through the skin, the following precautions should be followed until 24 hours after the last dose is given:

- Beginning 3 – 4 hours after the first dose, bathing with soap and water should be done 3 – 5 times per day and pat dry to avoid skin irritation.
- Change lines, clothes, and central line dressing after each bath
- Avoid moisturizer, barrier creams, antiperspirants, and deodorants during treatment

6 Required Observations (Appendix III A and III B)

6.1 Required observations are listed in Appendix III. The required observations for Transplant 1 (Appendix IIIA) will continue until 2 weeks before admission for Transplant 2 (Appendix IIIB).

6.1.1 If the patient is not eligible to move forward to Transplant 2 (see section 3.11) then all required observations for Transplant 1 will continue.

6.1.2 If the patient is eligible for Transplant 2 between day +30 and day +90, then the required observations for Transplant 2 will become effective at the time eligibility is determined. If the patient has had investigations performed (i.e. serum tumor markers on day +42) within the 2 weeks prior to admission for Transplant 2 (day +50 scheduled admission), these will not need repeated and the values obtained from the Transplant 1 observations will be used.

6.2 Staging studies prior to enrollment to define the extent of disease will include unilateral bone marrow aspiration and bilateral bone marrow biopsy, PET/CT scans of chest, abdomen, pelvis and brain, serum tumor markers including AFP, β-hCG, and LDH

If patient has had <u>no prior bone marrow involvement</u>, then bone marrow biopsies will be performed to determine eligibility and then at yearly intervals unless otherwise clinically indicated.

6.3 Imaging will be performed prior to enrollment in study; at Day +28, at Day +100, at Day +180, at 1 year and then at 6 month intervals in the second post-transplant year. Day +28 staging will be with a CT scan only. All other imaging will be with a PET/CT.

6.4 Serum tumor markers including AFP, β-hCG, and LDH will be checked every 2 weeks from transplant until day+100 and then at 6, 9, and 12 months post

transplant. After 1 year, tumor markers will be checked every 6 months until 2 years post-transplant.

7 Transplant Related Toxicities and Complications

7.1 G-CSF mobilization:

Frequency	Toxicity
Common	• Bone or muscle aches • Fever or chills • Discomfort at the injection site • Malaise
Uncommon	• Skin rash • Headache
Rare	• Polyserositis

7.2 Peripheral blood stem cell collections

Frequency	Toxicity
Common	• Mild discomfort at the site of catheter placement
Uncommon	• Hypotension • Thrombocytopenia might develop transiently following the leukopheresis and, if necessary, irradiated Blood Bank platelet concentrates will be transfused.

7.3 Chemotherapy Mobilization:

Cyclophosphamide (Cytoxan)	
Frequency	**Toxicity**
Common	• Nausea and vomiting (aggressive anti-emetic therapy may minimize) • Diarrhea • Alopecia usually reversible, but changes in hair color or texture after regrowth may occur • Permanent sterility is likely at this dose of cyclophosphamide, particularly when given with other drugs
Uncommon	• Skin rash • Hemorrhagic cystitis may occur following the use of cyclophosphamide despite aggressive fluid replacement, frequent voiding and Mesna

Rare	• Pericarditis • Cardiomyopathy: cyclophosphamide can cause fatal cardiac necrosis with clinical irreversible heart failure. • EKG changes are not infrequent and reduction in EKG voltage may be observed. Patients with compromised ejection fraction, previously treated with anthracyclines, or with mediastinal irradiation may be at higher risk.

Plus G-CSF (see section 7.1)

7.4 Transplant 1

Paclitaxel (Taxol)	
Frequency	**Toxicity**
Common	• Nausea and vomiting • Diarrhea • Mucositis • Alopecia
Uncommon	• Hypersensitivity reactions characterized by generalized skin rash, flushing, erythema, hypotension, dyspnea, and/or bronchospasm. Usually occurs within the first 2 – 10 minutes of infusion and is decreased by pre-meds • Transient Bradycardia • Peripheral Neuropathy - generally numbness and paresthesias
Rare	• Arrythmias including Mobitz I, Mobitz II, 3rd degree heart block, and Ventricular arrhythmias • Motor and autonomic neuropathies

Ifosphamide (Ifex)	
Frequency	**Toxicity**
Common	• Nausea and vomiting with associated anorexia. An aggressive anti-emetic regimen should be used including prophylactic serotonin antagonists plus dexamethasone prior to infusion. • Alopecia usually reversible but changes in hair color or texture after regrowth may occur
Uncommon	• Hemorrhagic cystitis may occur despite aggressive fluid replacement, frequent voiding, and Mesna
Rare	• Neurotoxicity including lethargy, confusion, weakness and hallucinations may occur. This is more common in patients with impaired renal function

Plus G-CSF (see section 7.1)

7.5 Transplant 2

Carboplatin (Paraplatin)	
Frequency	**Toxicity**
Common	• Nausea and vomiting • Hypocalcemia • Hypokalemia • Hypomagnesemia
Uncommon	• Peripheral neuropathy • Hyponatremia • Renal toxicity
Rare	• Allergic reaction with infusion presenting as a skin rash, urticaria (hives), and pruritis (itching)

Thiotepa (Thioplex)	
Frequency	**Toxicity**
Common	• Nausea and vomiting • Mucositis • Skin changes including rash, bronzing of the skin, erythema, flaking, and desquamation
Uncommon	• Allergic reaction including skin rash, hives, and rarely bronchospasm
Rare	• Hemorrhagic cystitis

Etoposide (VP-16)	
Frequency	**Toxicity**
Common	• Nausea and vomiting • Diarrhea • Mucositis
Uncommon	• Hypersensitivity reaction with chills and fever
Rare	• Bronchospasm during infusion • Hypotension (low blood pressure) during infusion

7.6 Myelosuppression

7.6.1 Both the chemomobilization and the pre-transplant conditioning (chemotherapy) induce significant myelosuppression requiring re-

infusion of viable hematopoietic stem cells for prompt hematologic recovery.

7.6.2 During the period of pancytopenia, the patient is highly vulnerable to infection and/or bleeding. Irradiated red cell transfusions will be given to maintain adequate oxygen delivery (hemoglobin > 8.0 gm/dL) and platelet transfusions will be given in an attempt to maintain a platelet count >10 x 10^9/L.

7.6.3 Prophylactic measures to reduce risks of infection and to vigorously treat any infections will also be required according to UMMC BMT ID guidelines.

7.7 Second malignancy

The potential carcinogenic effects of the pre-transplant chemotherapy and may compound the inherent risks of second malignancy already induced by treatment the patient may have already received. Both late second epithelial malignancies and early treatment-associated neoplasms (particularly myelodysplastic syndrome and/or leukemia) may develop after transplantation.

8 Adverse Event Reporting

Toxicity and adverse events will be classified according to NCI's Common Terminology Criteria for Adverse Events V 4.0 (CTCAE). A copy of the CTCAE can be downloaded from the CTEP home page (http://ctep.cancer.gov).

8.1 Reporting Requirements

For the purposes of this study, all subjects will be monitored at least monthly continuously for all serious unexpected and selected serious adverse events (SAE) during the first 100 days after cell infusion. SAEs include: graft failure (severe pancytopenia with a marrow cellularity <5% at day +28 post transplant), relapse, and death.

Toxicities, complications of therapy and other adverse events, which are considered expected as part of therapy in general, are listed in section 7 of the protocol.

In the event of an adverse event, the first concern will be for the safety of the subject. Investigators are required to contact the PI (Dr. Claudio Brunstein,) to discuss the event and subject care.

ADVERSE EVENT REPORTING REQUIREMENTS			
Unexpected Event*		**Expected Event***	
During first 100 days; grades 3 - 5	**After first 100 days; only death or selected SAE****	**During first 100 days; selected SAE****	**After first 100 days**
Report using UMCC SAE form	Report using UMCC SAE form	Report using UMCC SAE form	Knowledge of Death and relapse reported annually as part of study continuing review

* Unexpected Events are any toxicities, complications of therapy, and adverse events NOT appearing in the Transplant Related Toxicities and Complications Section 7 of protocol.

** Serious adverse events include: graft failure (severe pancytopenia with a marrow cellularity <5% at day +28 post transplant), relapse, and death.

Events that meet the reporting requirements should be simultaneously reported to the IRB and the Clinical Trials Office (CTO) within 10 working days.

The University of Minnesota Serious Adverse Event Report form may be downloaded from http://www.cancer.umn.edu/page/docs/sae.pdf

9 Data and Safety Monitoring

This study will be in compliance with the University of Minnesota Cancer Center's Data & Safety Monitoring Plan, which can be accessed at http://www.cancer.umn.edu/page/resource/dataplan.html

Regular meetings of the study's principal investigator and staff will be held to discuss matters related to the safety of protocol participants, validity and integrity of the data, enrollment rate, retention of participants, adherence to protocol, and data completeness.

The Principal Investigator will provide at least monthly monitoring of patient safety with attention to the stopping rules (section 10.5) with quarterly reporting to the Clinical Trials Office (CTO) for distribution to the Data and Safety Monitoring Council (DSMC).

At the time of the IRB continuing review, the Principal Investigator will submit to the CPRC a copy of all documentation submitted to the IRB for continuing review.

10 Experimental Design and Statistical Considerations

10.1 Primary Clinical Endpoint: Probability of one year survival for tandem AuSCT

10.2 Secondary Endpoints and Comparisons

10.2.1 Probability of one year disease-free survival for tandem AuSCT
10.2.2 Toxicity rate of tandem AuSCT
10.2.3 Probability of engraftment of neutrophils and platelets
10.2.4 Determine numbers of patients unable to adequately mobilize sufficient peripheral blood stem cells (PBSC) for tandem transplant
10.2.5 Identify prognostic factors of those patients unlikely to mobilize sufficient PBSC for tandem transplant
10.2.6 Compare outcomes of overall and disease free survival for patients undergoing single versus tandem transplant due to biologic randomization

10.3 Statistical Analysis

Survival and disease-free survival will be estimated by the Kaplan-Meier method. Engraftment will be estimated by cumulative incidence using competing risk methods. 95% confidence intervals will be used to make inferences. Comparison of survival and disease free survival between patients receiving single versus tandem transplant will be completed by the log-rank test or left descriptive depending on patient numbers. The toxicity rate and analysis of prognostic factors will be descriptive using proportions.

10.4 Sample Size Considerations

We only expect to enroll 2 to 4 patients per year over a five year period based on a SEER incidence rate of testicular cancer in 2003 of 5.3/100,000 with a higher incidence in Caucasians, our predominant population. Since AuSCT is considered a standard salvage therapy for relapsed GCT, these patients will be seen in our clinic and most will be anticipated eligible for this study. 50-60% of patients are expected to receive a tandem AuSCT. Assuming that we enroll the maximum number of 25, we will then have 15 patients among the tandem patients to get an estimate of the survival. Assuming a survival estimate of 0.5, the 95% confidence bandwidth will have a width of 0.5.

10.5 Stopping Rules

Monitoring guidelines for non-relapse mortality were developed using the sequential probability ratio test with the level of significance and power preset at 5% and 80% respectively. Monitoring guidelines will only be used for the tandem

AuSCT as single transplants have been shown to be safe in terms of non-relapse mortality.

Day 100 non-relapse mortality
Given a hypothesized non-relapse mortality rate of less than 5% and a maximum tolerated level of 15% among the tandem AuSCT, the trial will be halted and reviewed if 3 deaths occur in the 1st 3 evaluable patients, 5 deaths occur in the 1st 8 evaluable patients or 6 occur in the 1st 15 evaluable patients.

11 Retention of Records

The investigator will retain study records, including source data, copies of case report form, study drug receipt and dispensation, and all study correspondence indefinitely in a secured facility. 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.

Research data is collected in the BMT database indefinitely.

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Appendix I: International Germ Cell Cancer Consensus Classification

NON-SEMINOMAS	SEMINOMAS
Good Prognosis	
• Testicular or retroperitoneal primary AND • No non-pulmonary visceral metastases AND • Good Markers defined as (requires all) AFP < 1000 ng/mL hCG < 5000 IU/L LDH < 1.5 x Upper limit of normal	• Any primary site AND • No non-pulmonary visceral metastases AND • Markers AFP: normal hCG and LDH: normal or elevated
Intermediate Prognosis	
• Testicular or retroperitoneal primary AND • No non-pulmonary visceral metastases AND • Intermediate Markers defined as any of AFP 1000 – 10,000 ng/mL hCG 5000 – 50,000 IU/L LDH 1.5 – 10 x Upper limit of normal	• Any primary site AND • Non-pulmonary visceral metastases AND • Markers AFP: normal hCG and LDH: normal or elevated
Poor Prognosis	
• Mediastinal primary OR • Non-pulmonary visceral metastases OR • Poor Markers defined as any of AFP > 10,000 ng/mL hCG > 50,000 IU/L LDH > 10 x Upper limit of normal	• No patients with pure seminomas are classified as poor prognosis

Appendix II – Lansky and Karnofsky Performance Status

LANSKY (persons < 16 years old)		**KARNOFSKY** (persons ≥ 16 years old)
Fully active, normal	100	Normal no complaints; no evidence of disease.
Minor restrictions in physically strenuous activity	90	Able to carry on normal activity; minor signs or symptoms of disease.
Active, but tires more quickly	80	Normal activity with effort; some signs or symptoms of disease.
Both greater restriction of and less time spent in play activity	70	Cares for self; unable to carry on normal activity or to do active work.
Up and around, but minimal active play; keeps busy with quieter activities	60	Requires occasional assistance, but is able to care for most of his personal needs.
Gets dressed but lies around much of the day, no active play but able to participate in all quiet play and activities	50	Requires considerable assistance and frequent medical care.
Mostly in bed; participates in quiet activities	40	Disabled; requires special care and assistance.
In bed; needs assistance even for quiet play	30	Severely disabled; hospital admission is indicated although death not imminent.
Often sleeping; play entirely limited to very passive activities	20	Very sick; hospital admission necessary; active supportive treatment necessary.
No play; does not get out of bed	10	Moribund; fatal processes progressing rapidly.
Unresponsive	0	Dead

Appendix IIIA:
Required Observations Transplant 1

	within 30 days of enrollment	Prior to Admit for transplant	day +14	day +28	day +42	day +60	day +74	day +88	** day +100	day +180	9 mo	1 yr	18 mo	2yr
Medical History	x	x												
Physicial Exam	x	x		x		x			x	x		x	x	x
Weight/Height	x	x												
Performance status	x	x		x		x			x	x		x	x	x
Adverse Event/toxicity notation	x	x		x		x			x	x		x	x	x
Comprehensive chemistry panel	x	x		x		x			x	x		x	x	x
Hepatic Panel	x	x		x		x			x	x		x	x	x
CBC with diff	x	x		x		x			x	x		x	x	x
AFP	x	x	x	x	x	x	x	x	x	x	x	x	x	x
LDH	x	x	x	x	x	x	x	x	x	x	x	x	x	x
β-hCG	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Viral Hepatitis serologies	x											x		
Quantitative Immunoglobulin	x								x	x		x		
pb $CD4^+$	x								x	x		x		
pb $CD8^+$	x								x	x		x		
CT scan – chest, abdomen, pelvis, and head. PET/CT will be done at all timepoints except d+28.	x			x					x	x		x	x	x
Bone Scan	x									x		x	x	x
MRI brain (if prior CNS lesions)	x			x					x			x		
Bilateral bm biopsy unilateral aspirate	x											x		x
BM Cytogenetics	x											x		x

An attempt should be made to obtain the scheduled activity as close as possible to the scheduled date. However, scheduling difficulties (for procedures and around weekends) may make this difficult. Therefore, the scheduled activity will be obtained within 14 days of that schedule (30 days for dates after day +100).

**For patients NOT having a second transplant, all follow-up procedures will continue out to 2 years based on the Required Observations table for Transplant 1. For patients having a second transplant, required observations will be per the Required Observations table for Transplant 2 and no further Transplant 1 observations will be collected.

Appendix IIIB:
Required Observations Transplant 2 (This will start between day +30 and day +90 from transplant 1)

	Within 2 wks of planned admission	day +14	day +28	day +42	day +60	day +74	day +88	day +100	day +180	9 mo	1 yr	18 mo	2yr
Medical History	x												
Physicial Exam	x		x		x			x	x		x	x	x
Weight/Height	x												
Performance status	x		x		x			x	x		x	x	x
Adverse Event/toxicity notation	x		x		x			x	x		x	x	x
Comprehensive chemistry panel	x		x		x			x	x		x	x	x
Hepatic Panel	x		x		x			x	x		x	x	x
CBC with diff	x		x		x			x	x		x	x	x
AFP	x	x	x	x	x	x	x	x	x	x	x	x	x
LDH	x	x	x	x	x	x	x	x	x	x	x	x	x
β-hCG	x	x	x	x	x	x	x	x	x	x	x	x	x
Viral Hepatitis serologies	x										x		
Quantitative Immunoglobulin	x							x	x		x		
pb $CD4^+$	x							x	x		x		
pb $CD8^+$	x							x	x		x		
CT scan – chest, abdomen, pelvis, and head. PET/CT will be done at all timepoints except d+28.	x		x					x	x		x	x	x
Bone Scan									x		x	x	x
MRI brain (if prior CNS lesions)	x		x					x			x		
Bilateral bm biopsy unilateral aspirate											x		x
BM Cytogenetics											x		x

An attempt should be made to obtain the scheduled activity as close as possible to the scheduled date. However, scheduling difficulties (for procedures and around weekends) may make this difficult. Therefore, the scheduled activity will be obtained within 14 days of that schedule (30 days for dates after day +100).

APPENDIX IV: RECIST Criteria

Response Criteria

Evaluation of target lesions *

Complete Response (CR):	Disappearance of all target lesions
Partial Response (PR):	At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Evaluation of non-target lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions **

* Target lesions: any lesion measurable prior to therapy. Lesions must be ≥ 1cm in longest diameter at time of disease evaluation prior to autologous transplant.

**Although a clear progression of "non target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).