Investigator Initiated Trial

Phase II HBO Auto-HSPC for MM

HBO effects on blood count recovery and post-transplant outcomes following high-dose therapy and autologous HSPC transplantation for multiple myeloma

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Principal Investigator (PI) Name: _____

PI Signature: _____

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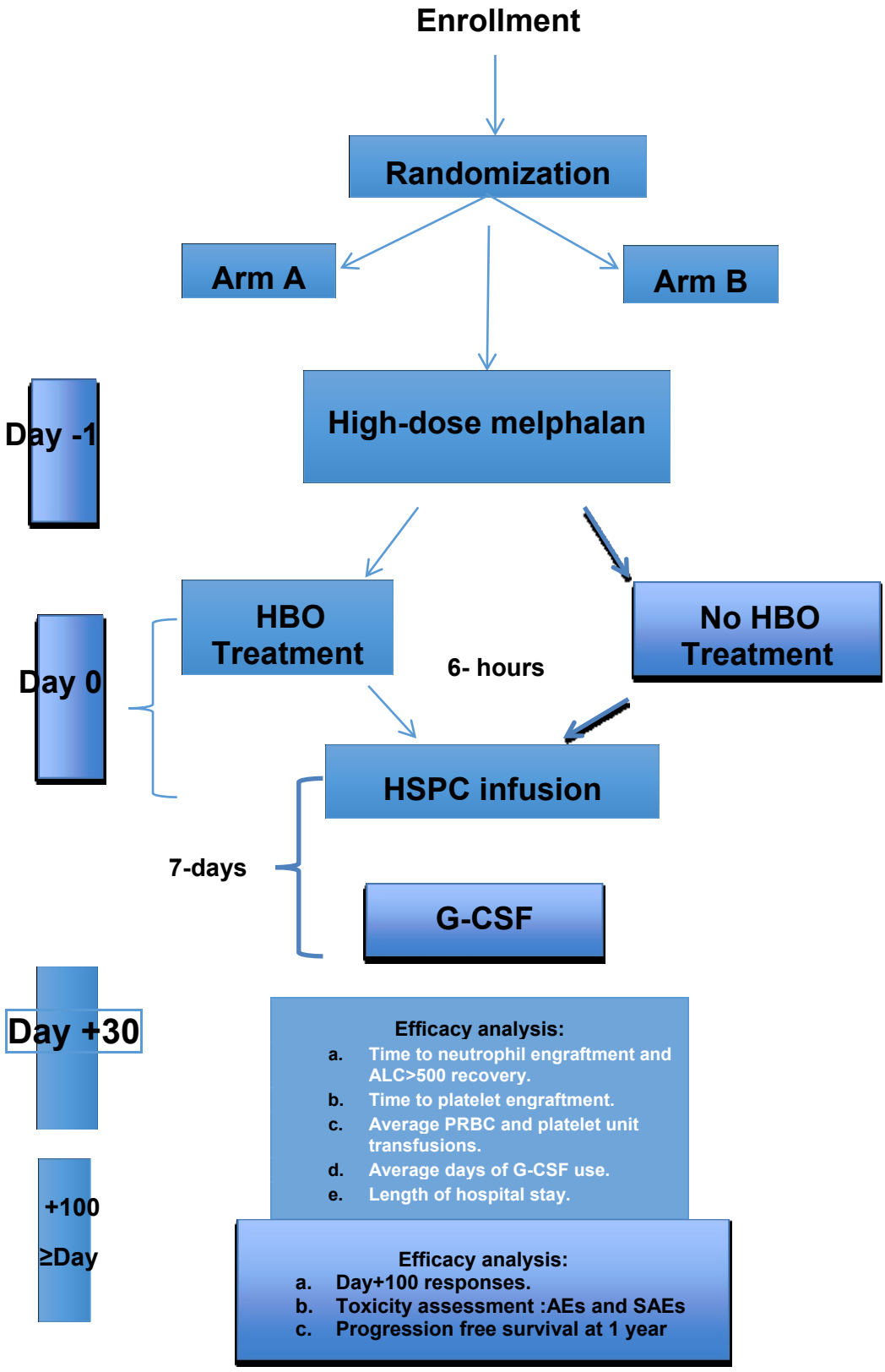
LIST OF ABBREVIATIONS

ATM	atmospheric pressure
DLCO	diffusing capacity of the lung for carbon monoxide
EPO	erythropoietin
FEV1	forced expiratory volume in one second
FVC	forced vital capacity
G-CSF	granulocyte-colony stimulating factor
GVHD	graft versus host disease
HBO	hyperbaric oxygen
HPCs	hematopoietic progenitor cells
HSCs	hematopoietic stem cells
MM	multiple myeloma
HSPC	Peripheral Blood Stem Cell
SDF-1	stromal-derived factor 1

STUDY SCHEMA



STUDY SUMMARY

Title	HBO effects on blood count recovery and post-transplant outcomes following high-dose therapy and autologous HSPC transplantation for multiple myeloma
Short Title	2017-IIT-Phase II Eval HBO in AutoHSPC for MM
Phase	Phase 2
Methodology	Randomized to either HBO therapy or no HBO therapy prior to HSPC infusion
Study Duration	2 years
Study Center(s)	Wilmot Cancer Institute University of Kansas Medical Center University of Kentucky (UK), Markey Cancer Center (MCC)
Objectives	**Primary Objective**: Evaluate the effect of HBO on blood count recovery following high-dose therapy and autologous transplantation for multiple myeloma. **a)** Evaluate time to ANC recovery post-transplant. **b)** Evaluate time to platelet recovery post-transplant. **c)** Evaluate ALC recovery through day 15 post-transplant. **d)** Evaluate the average number of PRBC transfused units during the first 30 days of transplant. **e)** Evaluate the average number of platelet units transfused during the first 30 days of transplant. **f)** Evaluate the average days of G-CSF use post-transplant. **Secondary Objective**: Examine the effect of HBO on disease response post-autologous transplantation. a) Evaluate the effect of HBO on day 100 responses in patients undergoing transplant and correlate that to early ALC recovery. b) Progression free survival at one year post-transplant **Exploratory Objective (Correlative Studies)**: Explore HBO effects on plasma/serum EPO and IL-15 post-high dose therapy and autologous transplantation. a) Explore HBO effects on plasma/serum EPO and IL-15. b) Explore HBO effects on NK cell recovery c) Evaluate the effects of HBO on IL-15 response post-transplant (pre-chemo, day 0 pre and post HBO, day 3 post-transplant, weeks 1 and 2 post-transplant) and correlate that to early ALC recovery and disease response.

Number of Subjects	Up to 115 patients to enroll to reach a 100 evaluable subjects in total between URMC, KUMC, and UK-MCC Up to 90 patients to enroll over 3.5 years at URMC to reach an 80 evaluable subjects Up to 25 patients to enroll over 3.5 years at KUMC and UK-MCC to reach 20 evaluable subjects
Diagnosis and Main Inclusion Criteria	Patients with multiple myeloma who are considered for high-dose therapy and autologous transplant.
Study Product(s), Dose, Route, Regimen	For subjects that are randomized to the HBO arm, HBO treatment will be administered on day 0 of the transplant, around 9:00 am. The treatment consists of exposure to hyperbaric oxygen at 2.5 ATA for a total of 90 minutes, in a single see-through hyperbaric chamber, breathing 100% oxygen. During the 90 minutes, there will be two breaks for 10 minutes each in which subjects will be breathing compressed environmental air (21% oxygen). There will be an additional 15 minutes spent during compression at the initiation of therapy and 15 minutes spent for decompression at the end. **HSPC infusion:** 6-hours from the start of HBO therapy, HBO patients will receive HSPC unit infusion approximately at 3pm. Non-HBO patients will receive HSPC infusion at 3pm. Institutional guidelines will also be followed in terms of pre-medications and Auto HSPC unit infusions for both cohorts
Duration of Administration	120 minutes (90 minutes actual HBO))
Reference Therapy	Standard reference is no HBO therapy
Interim Monitoring	The study will be monitored bi-annually by DSMC at Wilmot Cancer Institute and interim monitoring will include safety. The study will be approved by the IRB at each institution prior to enrollment. Local IRB guidelines will be followed for AE and SAE reporting.

Statistical Methodology	**Primary Objective**: The primary endpoint of the study is time from transplant to neutrophil recovery. We expect no loss to follow-up or death prior to neutrophil recovery, and expect to observe neutrophil recoveries in all patients. Our assumptions are based largely on a recent single-arm study of hyperbaric oxygen in ASCT (REF). We hypothesize that HBO will increase the relative hazard of neutrophil recovery by 80%, corresponding to a hazard ratio (HR) of 1.8. This corresponds with a decrease in proportion who have not had a neutrophil recovery at 10 days from 81% to 68%, or alternatively, an increase in 10 day neutrophil recovery from 19% to 32%. 100 subjects (50 per arm) provides 81% power to detect HR=1.8 at a two-sided α=0.05 level of significance. Subjects will be 1:1 block-randomized, with random block sizes of 4 and 6.The primary analysis will be based on a 1- degree of freedom (1-df) likelihood ratio test (LRT) of HBO treatment in the actually infused cell dose-stratified Cox model. As we expect many ties in recovery time, the exact method will be used to handle ties in the Cox model. The HR for HBO will be reported along with a 95% confidence interval (CI) and associated LRT p-value. Time to neutrophil recovery by HBO group will be summarized graphically via the Kaplan-Meier method. **Secondary Objective**: Secondary endpoints will include time to platelet recovery, time to absolute lymphocyte count recovery, days of G-CSF use, PRBC units received, platelet units received, length of hospital stay, and disease response at 100 days posttransplant. Time to event outcomes will be analyzed using methods detailed above. Continuous outcomes will be compared between groups using the non-parametric Wilcoxon rank-sum test, and binary outcomes will be compared using Fisher's exact test. **Exploratory Objective (Correlative Studies):** To explore HBO effects on IL-15 and EPO responses, we will use a linear mixed model (and model diagnostics described above for assessment) with treatment group as the explanatory measure of interest

1.0 BACKGROUND AND RATIONALE

High-dose chemotherapy with or without radiation combined with autologous peripheral blood stem cell (HSPC) transplantation is considered a curative option for patients with a myriad of hematological malignancies including Hodgkin's disease[1] and non-Hodgkin's lymphoma (NHL).[2] Data also supports improved survival in patients with relapsed follicular lymphoma who receive autologous HSPC transplantation.[3] Additionally, it is considered part of standard of care treatment strategy in patients with multiple myeloma (MM)[4]. Though high-dose chemotherapy and HSPC transplantation is considered a curative procedure, patients who undergo this treatment regimen suffer from multiple morbidities and potential mortality due to complications that arise as a result of chemo/radiation therapy-induced bone marrow suppression.

Morbidity and mortality related to high-dose chemotherapy and autologous HSPC transplantation.

High-dose chemotherapy/radiation-related complications include: mucositis, neutropenia, and neutropenic fever. In one prospective study, the incidence of severe oral mucositis (World Health Organization (WHO) grades 3 to 4) was 46% in patients with MM and 42% in patients with NHL,[5] with a mean duration of severe mucositis of 5.3 days in MM patients and 5.5 days in NHL patients. This complication seems to be associated with higher chemotherapy dose per kilogram of body weight.[5] Depending on the severity of mucositis, some patients will require tube feeding for nutritional support and opioid analgesics for pain control.[6] Additionally, oral ulcers increase the risk of febrile neutropenia and infection risk.[6,7] These complications, obviously, negatively impact the clinical of the transplant and increase the economic burden of the transplant.[6] However, infectious complications remain the most common cause of early mortality post-autologous HSPC transplantation. In a retrospective study 83% of autologous HSPC transplantation patients developed at least one neutropenic fever episode; 5% developed severe sepsis, and 3% developed severe sepsis requiring intensive care unit admission.[8] In that study, the duration of neutropenia was a risk factor for severe sepsis. In addition, thrombocytopenia necessitates platelet transfusions, adding to potential complications and to increased cost of transplant. For example, the average 60-day platelet transfusion cost per patient undergoing autologous HSPC transplantation was estimated to be around $4,000.[9]

Interventions to help reduce post-transplant complications and economic impact. The use of colony-stimulating factors post-transplant clearly results in shortened neutropenia, hospitalization and reduced overall cost.[10,11] Also, growth factor use might be associated with reduced mucositis.[12] The move to performing Auto-HSPC transplantation as an outpatient procedure is another way to help reduce the overall transplant cost.[13] However, a substantial percentage of those transplanted as outpatient will be eventually admitted to the hospital; in one series of studies, this percentage was 60%.[14] The major side effects that trigger hospital admission include neutropenic fever and mucositis necessitating narcotic usage. These two complications are related to the direct effect of *chemotherapy and/or radiation on hematopoietic tissue and the gastrointestinal tract, but are reversible upon neutrophil recovery.*

Statement of need for further interventions to help with post-transplant complications. Interventions are warranted to further help shorten neutropenia post-high-dose chemotherapy and Auto-HSPC transplantation. Such interventions will ultimately help reduce the transplantrelated mortality and morbidity related to infectious complications and mucositis. Additionally, such interventions will potentially reduce days of hospitalization, transfusions, antibiotic use, and narcotic use for mucositis. As such, it will reduce the overall cost of Auto-HSPC transplantation.

Blood count recovery following HSPC transplantation: Relationship to erythropoietin.

Earlier observations implicated erythropoietin (EPO) in HSPC homing, in which circulating

Table-1: Time to count recovery in HBO and historic cohorts.			
	HBO Cohort (n=20)	**Historic Cohort (n=225)**	***P*-value**

Time to neutrophil recovery, mean in days (Range)	10.7 (9-13)	11.3 (7-18)	0.04
Time to platelet recovery, mean in days (Range)	16.2 (14-21)	19.8 (11-86)	0.04

HSPCs actively cross the blood/bone marrow endothelium barrier and lodge (at least transiently) in the bone marrow compartment.[15] HSPC homing to bone marrow is a step that precedes engraftment, which corresponds to the proliferation and differentiation of HSPCs to produce mature, functional hematopoietic cells within the bone marrow.[16] Gonzalez et al. demonstrated that *in utero,* circulating HSPCs rapidly decline after birth. [17] Interestingly, the decline in HSPCs correlated with low EPO blood concentration. The authors speculated that the decline in HSPCs was explained by HSPC bone marrow homing. These observations suggested a possible role for EPO in bone marrow homing process. Intrigued by this observation, we investigated the role of EPO in UCB HSPC homing and engraftment as UCB HSPCs experience defects in bone marrow homing.[18] We demonstrated that a large HSPC population of UCB HSPCs (~46%) express cell surface EPO receptor (EPOR), and that their exposure to EPO inhibits UCB $CD34^+$ cell *in vitro* transmigration.[18] The effect of such inhibited migration was reversed by either depleting EPOR expression on UCB $CD34^+$ cells, or through blocking EPO or EPOR by neutralizing antibodies. Recognizing the negative effects of EPO on HSPC transmigration and possibly homing, we investigated hyperbaric conditions as an intervention to lower EPO to improve HSPC homing, as hyperbaric oxygen (HBO) is known to reduce EPO in healthy volunteers.[19] HBO therapy involves inhalation of 100% oxygen intermittently under a pressure greater than 1 atmosphere (ATM), which results in both mechanical effects related to increased pressure and physiologic effects related to hyperoxia[46]. Our in vivo studies showed that HBO conditions promoted homing of transplanted UCB HSPC to the bone marrow by reducing systemic EPO levels in the recipient.[18] We also evaluated the impact of HBO on UCB HSPC homing in a murine transplant model. In these experiments, irradiated mice that received HBO treatment prior to UCB cell infusion, showed significantly improved myeloid, B-cell and T cell engraftment in comparison to non-treated mice. [20] In a pilot clinical trial, we also have demonstrated that HBO therapy given as a single treatment 6 hours prior to UCB transplantation was well-tolerated and resulted in significant reduction in median EPO level from baseline. Compared to historic controls, median time to neutrophil recovery was shorter in HBO- treated patients (14 vs 20.5 days). Also, all HBO patients had complete platelet

Table-2: HBO effects on high-dose therapy and auto HSPC transplant outcomes.

	HBO Cohort (n=19)	**Historic Cohort (n=118)**	***P*-value**
Days G-CSF use	6.21 (4-9)	9.16 (5-19)	0.0007
Mucositis incidence **Grade 1** **Grade 2** **Grade 3** **Grade 4**	5 (26.3%) 0 4 (21.1%) 1 (5.2%) 0	70 (59.3%) 14 (12.2%) 44 (37%) 12 (10.1%) 0	0.008
PRBC units transfused	2.1(1-7)	2.58(1-7)	0.22
Platelet units transfused	2.5 (1-12)	3.2(1-21)	0.17
Neutropenic fever	9 (47%)	77 (65%)	0.11

recovery as compared to only 69% of controls (*p*=0.013) and these HBO-treated patients achieved transfusion independency (TTI) earlier than the controls.

Pilot clinical trial indicate safety and feasibility of HBO in autologous HSPC transplantation.

Based on these results, we initiated a pilot study in autologous HSPC transplantation. A total of 20 patients were treated on the autologous HSPC transplant study. HBO therapy was very well tolerated as 19 completed full therapy. In terms of blood count recovery, our preliminary data indicate an average time to neutrophil count recovery of 10.7 days compared to 11.3 days (P=0.04) and average time to platelet count recovery of 16.2 days compared to 19.8 historically (p=0.04). In a separate analysis, we evaluated HBO effects on other outcomes post- autologous transplantation. In this analysis, we compared our HBO cohort patients who completed HBO therapy (n=19) with our historic patients (n=118). We found that the average days of GCSF use was 6.2 days in the HBO cohort compared to 9.16 days in controls (P=0.0007). HBO patients had significantly less mucositis (26.3% vs 53.3%, *p*=0.008). The average number of transfused packed red cell units was 2.1 and 2.58 units (P=0.22), while platelet units transfused was 2.5 and 3.2 (P=0.17) in the HBO and historic cohorts, respectively. Biologically, a positive correlation between HBO mediated reduction in EPO levels and time to neutrophil recovery was observed in our HBO cohort (p = 0.05).

HBO and ALC recovery in Auto-HSPC pilot clinical incorporating HBO.
We also evaluated ALC recovery post Auto-HSPC in our HBO study, as early ALC recovery is another sign of early HSCP engraftment and early ALC recovery was found to be associated with improved survival post-transplant. This effect was seen in patients with mantle cell lymphoma[21], multiple myeloma (MM) [22, 23], amyloidosis[24], Non-Hodgkin lymphoma (NHL) [25], Hodgkin's disease (HD)[26] and even acute myeloid leukemia[27]. Though the definition of early ALC varies between studies, most of these studies define early ALC recovery as recovery of lymphocyte count to 500 cells/microL on day 15.[23] Applying this definition, a study showed that the median overall survival (OS) for MM patients was 33 months in patients with early ALC recovery compared to 12 months in patient with late ALC recovery (P <.0001). Similarly, progression free survival (PFS) was longer in patients with early versus late ALC recovery (16 vs 8 months, P <.0003). Also, for patients with NHL, the PFS time was significantly longer in patients with early ALC recovery than later ALC (not reached vs 4 months, P <.0001). In that study, multivariate analysis demonstrated that early ALC recovery was an independent prognostic indicator for PFS for both patients with MM and NHL. In our HBO experience, early ALC recovery was observed in 13/17 (76%) of assessable patients with all patients achieving ALC of 500 by day 18 post-transplant. In our preliminary data, the median time to achievement of early ALC was 12 (8-18) days. These data are encouraging as early ALC is seen in approximately 50% of patients with MM or NHL receiving high-dose therapy and autologous transplant.[23]

IL-15 and early ALC recovery following high-dose therapy and autologous Transplantation.
Though the basic mechanism for such improvement in OS and PFS in patients with early ALC recovery has not been deeply investigated, evidence suggests that it is related to early recovery of Natural Killer (NK) cell subset[28,29] mediated by interluken-15 (IL-15).[28] The role of NK cells in improving survival post autologous transplant has led to several clinical trials utilizing NK

cellbased mechanisms to reduce disease relapse. For example, the use of FLT-3 ligand was found to induce dendritic cells and subsequently NK cells post-transplant.[30] In another study, IL-2 and interferon-α combination was investigated as a modality to increase NK cells post autologous transplant.[31] Others also investigated the use of NK cells for ex vivo purging of autologous graft.[32] These approaches are costly and are associated with graft manipulation. *Simpler approaches are warranted to increase early NK and ALC recovery to reduce relapse postautologous transplantation. In this application, we propose the use of hyperbaric oxygen (HBO) as a modality to facilitate early ALC recovery post-transplant.*

HBO and IL-15 in autologous HSPC pilot clinical incorporating HBO.

As NK subset recovery has been shown to be mediated by interluken-15 (IL-15), [28] we evaluated IL-15 blood levels in patient who underwent autologous HSPC transplantation on our pilot HBO study. We evaluated plasma IL-15 levels at different time points; the day of starting preparative regimen (day -6 for lymphoma subjects and day -3 for myeloma subjects), the morning of HBO treatment (day 0), and 6, 24, and 48 hours after starting HBO treatment. We also evaluated Il-15 level at the third day of engraftment (Figure-1). In preliminary data we have observed the following: a.IL-15 level was significantly higher on day 0 prior to HBO therapy compared to baseline level; b.IL-15 level was significantly higher 48-hours following HBO therapy compared to day 0, pre-HBO levels, c. third day of engraftment IL-15 levels were significantly higher than baseline levels. To add, on the third day of engraftment (on average day 13 post-transplant), average IL-15 levels was 2.87X the baseline value. In one published study, day 14 IL-15 was almost 2X its baseline level in a study that utilizes co-stimulated T cells to facilitate immune recovery.[33] Accordingly, our preliminary data suggest that IL-15 might be higher in our study cohort than historic data (2.87X vs 2X) and suggests a possible role for HBO in inducing higher IL-15 blood levels. *On other hand, there is no published data examining the effects of HBO on IL-15 and such studies are warranted*. This is especially important since IL-15 blood level was found to correlate with patient survival following high-dose therapy and autologous transplantation.[28] The effect might be even more profound, as data suggest that in a subset of patients with follicular lymphoma and MM, autologous HSPC transplantation might be associated with prolonged PFS or might be even curative. [34,35]

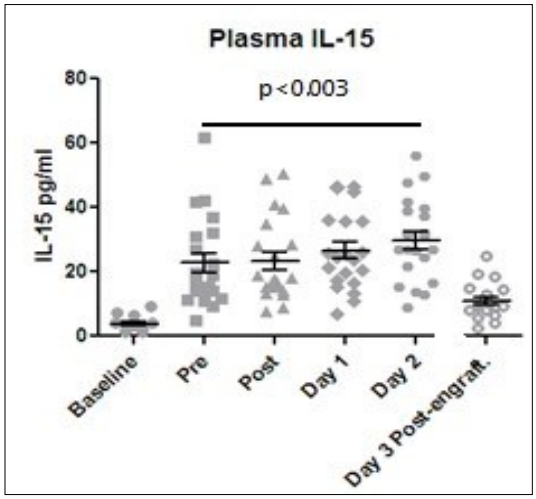


Figure-1: HBO effects on IL-15 in our pilot study in autologous

Hypothesis:

Based on our preliminary data, our central hypothesize is that HBO therapy significantly reduces post-transplant EPO and as a result improves HSPC engraftment evident by improved time to neutrophil, platelet, and early ALC recovery in MM patients undergoing high-dose therapy and autologous transplantation (Figure-2). We also hypothesize that HBO therapy up-regulates IL-

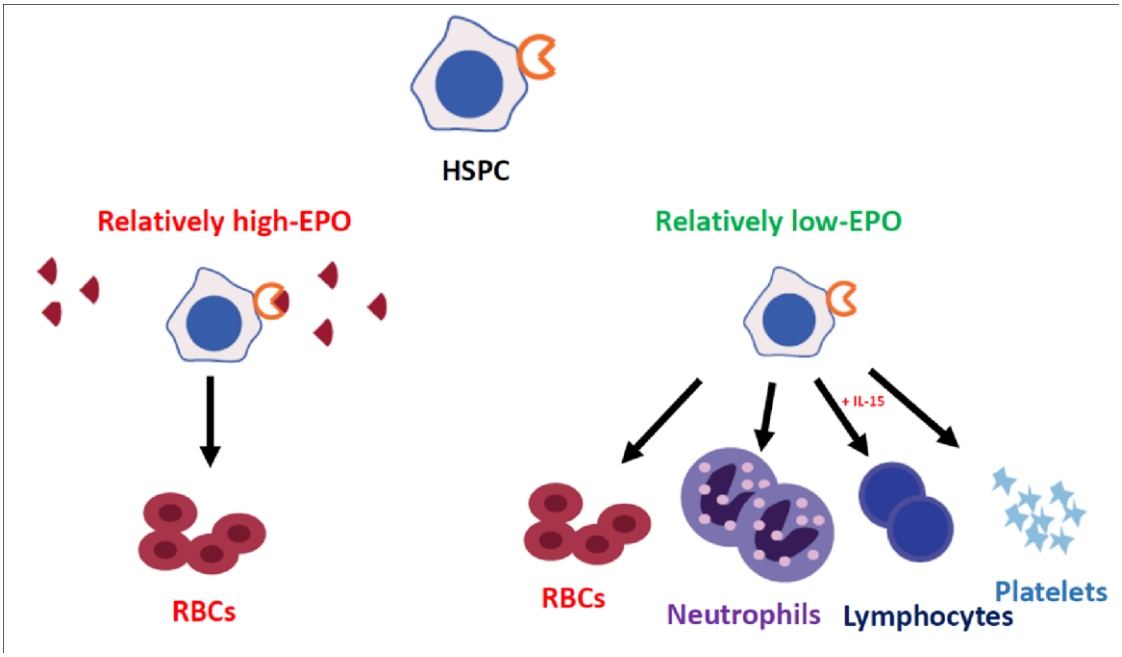


Figure-2: The effects of low EPO environment induced by HBO on HSPC engraftment potential. *(RBC: red blood cells and IL-15: interleukin-15)*

15 day 15 post-transplant and as a result further enhances ALC recovery in MM patients undergoing HSPC transplantation (Figure-2).

Innovation:
The use of HBO to improve blood count recovery and to reduce growth factor use, transfusion needs, and to shorten hospital stay in MM patients undergoing high-dose therapy and AutoHSPC transplantation represents an innovative approach as it targets the host microenvironment without manipulating the graft or use of pharmaceuticals, cell therapy or immune-modulators. Given the simplicity of the approach, it has the potential to result in a paradigm shift in how we deliver high-dose therapy and autologous transplantation. The result of this simple and well-tolerated intervention can be far reaching as it has the potential to improve ALC recovery and consequently the outcome of high-dose therapy and autologous transplantation by reducing disease relapse and improving survival of patients. This approach will have a major impact on multiple malignancies beside MM, like NHL and HD.

2.0 STUDY OBJECTIVES

In this phase II randomized clinical trial study, we will estimate the effect sizes of HBO therapy in improving neutrophil count recovery (primary), platelet count recovery and ALC recovery, and growth factor use, transfusion requirements, and hospital stay post high-dose therapy and autologous transplantation for MM.
Briefly, half of the participants in this study will be receiving one HBO therapy session prior to HSPC infusion and will be followed closely until day+100 with final assessment at 1 year. Our primary end point is time to neutrophil recovery in HBO treated subjects and in control subjects

not receiving HBO. As secondary end points we will determine platelet count recovery and ALC recovery, growth factor use, transfusion requirements, and hospital stay post high-dose therapy and autologous transplantation for MM. In addition, we will evaluate day 100 disease responses and 1 year PFS and explore the HBO effects on EPO and IL-15 cytokine levels post-transplant in both the HBO treated and control subjects.

2.1 Primary Objectives

2.1.1 Evaluate the effect of HBO on blood count recovery following high-dose therapy and autologous transplantation.

a. Evaluate ANC recovery post-transplant.
b. Evaluate platelet count recovery post-transplant.
c. Evaluate ALC recovery day 15 post-transplant.
d. Evaluate the average number of PRBC transfusions post-transplant.
e. Evaluate the average number of platelet transfusions post-transplant.
f. Evaluate the number of days of G-CSF use post-transplant.
g. Evaluate the length of hospital stay.

2.2 Secondary Objectives

2.2.1 Examine the effect of HBO on disease response post-autologous transplantation.

a. Evaluate the effect of HBO on day 100 responses and 1 year PFS in patients undergoing transplant.

2.3 Exploratory Objectives (Correlative Studies)

2.3.1 Explore HBO effects on plasma/serum EPO and IL-15 and NK cell recovery posthigh dose therapy and autologous transplantation.

2.3.2 Evaluate the effects of HBO on plasma/serum EPO and IL-15 response posttransplant
(pre-chemo, day 0 pre and post HBO, day 3 post-transplant, weeks 1 and 2 posttransplant) and correlate that to early ALC recovery and disease response.

2.4 Endpoints

Primary Endpoint:
Our primary end point is time to neutrophil count recovery in HBO treated subjects and in control subjects not receiving HBO.
Secondary Endpoints:

As secondary end points we will determine time to platelet count recovery, time to ALC recovery, PRBC and platelet transfusions, days of G-CSF use, lengthy of hospital stay, day 100 disease responses, and 1-year PFS. We will explore HBO effects on EPO and IL-15 cytokine levels and NK cell recovery post-transplant in both the HBO treated and control subjects.

3.0 PATIENT ELIGIBILITY

3.1 Inclusion Criteria

Subjects must meet all of the inclusion criteria to participate in this study.

Primary Objective Study population: Patients with MM who are considered for high-dose therapy and autologous transplantation at the bone marrow transplant clinic at the Wilmot Cancer Institute (WCI) will be screened for eligibility to enroll in this study and if eligible will be approached to participate. Eligible patients will have the chance to tour the hyperbaric oxygen facility prior to signing the consent form. Patients who agree to proceed will sign a written consent. The inclusion and exclusion criteria are listed below:

3.1.1 Voluntary written informed consent

3.1.2 Multiple myeloma diagnosis applying the latest criteria by IWG [36]. Patients should have received myeloma-directed induction therapy with appropriate response (PR or better) in newly diagnosed myeloma patients. Multiple myeloma patients who relapse following induction therapy or following prior Auto-HCT are also eligible as far as remission following their first Auto-HCT lasted 12 months or more.

3.1.3 Patients who are considered for high-dose therapy and autologous transplantation at the bone marrow transplant clinic at WCI will be screened for eligibility to enroll in this study and if eligible will be approached to participate. Eligible patients will have the chance to tour the hyperbaric oxygen facility prior to signing the consent form.

3.1.4 Subjects must be ≥ 18 years old and ≤ 75 years old

3.1.5 Karnofsky performance status (KPS) of ≥ 70% (Appendix A).

3.1.6 Adequate hepatic, cardiac and pulmonary function to be eligible for transplant. Minimum criteria include:

- ALT, AST: < 4x IULN
- Total bilirubin: ≤ 2.0 mg/dL
- EF measured by 2D-ECHO or MUGA scan of ≥ 45%
- FEV1, FVC and DLCD ≥ 50% of predicted value (corrected to serum hemoglobin) - EKG with no clinically significant arrhythmia.

3.1.7 Patients should have New York Heart Association (NYHA) Functional Classification, classI(ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain)or Class II (ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain).

3.1.8 Patients should be evaluated for fitness for HBO by a hyperbaric oxygen trained medical professional who is not part of the study team prior to starting preparative regimen.

3.1.9 Women of child-bearing potential should have a negative urine or serum pregnancy test within 4 weeks of starting preparative regimen.

3.1.10 Women of child-bearing potential and men with partners of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for 30 days following completion of therapy. Should a woman or partner become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician and the investigator immediately.

3.1.10.1 A woman of child-bearing potential is any female (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:

- Has not undergone a hysterectomy or bilateral oophorectomy; or
- Has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months)

3.2 Exclusion Criteria

Subjects meeting any of the exclusion criteria at baseline will be excluded from study participation.

3.2.1 Pregnant or breastfeeding

3.2.2 Severe chronic obstructive pulmonary disease requiring oxygen supplementation

3.2.3 History of spontaneous pneumothorax

3.2.4 Active ear/sinus infection. Patients with hronic sinusitis or sinus headaches are excluded unless cleared by ear,nose,throat consult

3.2.5 Recent sinus surgery (within the last 5 years) or ear surgery, excluding myringotomy or ear tubes

3.2.6 Claustrophobia

3.2.7 History of seizures

3.2.8 Evidence of pneumothorax or significant pulmonary fibrosis on chest imaging within 60 days of transplant.

3.2.9 Prior chest surgery that involved thoracotomy or prior direct irradiation to the lungs

3.2.10 Patients who had intrathecal chemotherapy within 2 weeks of starting preparative regimen or cranial irradiation within 4 weeks of starting preparative regimen

3.2.11 Active infection (viral, fungal, and/or bacterial)

3.2.12 Positive screening for Hepatitis A, B, or C indicating an ongoing infection

3.2.13 No active tobacco use 72 hours prior to transplant until complete transplant recovery.

4.0 TREATMENT PLAN

4.1 Treatment Dosage and Administration

Preparative regimens prior to HBO therapy:

Melphalan 200mg/M^2 given intravenously (IV) on day -1. For patients 70 years or older and/or those with serum creatinine ≤ 2.0 mg/dL, a lower melphalan dose of 140 mg/M^2 can be given intravenously (IV) on day -1, under the discretion of the treating physician.

4.2 Hyperbaric oxygen (HBO) treatment:

HBO treatment will be administered as either outpatient (WCI and KUCC patients) or inpatient (KUCC patients) on the morning of the stem cell transplant (Day 0), around 9am. The treatment consists of exposure to hyperbaric oxygen at 2.5 ATA for a total of 2 hours, in a single see-through hyperbaric chamber, breathing 100% oxygen while subjects are resting in supine position. During the 2 hours, there will be compression and decompression phases for 15 minutes each in which subjects will be breathing compressed environmental air (21% oxygen). Subjects will be able to communicate with the treating nurse and treatment will be stopped immediately, temporarily or permanently, in the event the treated subject develops any acute complications, or upon his/her request. For WCI patients, the treatment will be conducted as outpatient in the hyperbaric medicine unit at the Strong Wound Healing Center; University of Rochester Medical Center, 160 Sawgrass Drive, Rochester, NY 14620. WCI patients are responsible for transporting themselves to and from this location and given instructions on where to go before and after HBO therapy. In the case of using sedatives prior to outpatient HBO therapy, the patient will be asked to arrange for someone else to drive them to and from the Strong Wound Healing Center. The HBO device and the duration and specifications (pressure and % FiO2) of HBO therapy are the same as described in IND#17373.The unit is directed by Howard Langstein, M.D, who is a collaborator in this study. Patients will be admitted following HBO therapy to WCI for HSPC infusion and posttransplant care. For KUCC patients, the HBO treatment will be done as inpatient or outpatient using Sechrist Industries model 3200/3200R at KUMC's Hyperbaric Medicine unit. If HBO therapy is performed outpatient at KUMC, patients are responsible for transporting themselves to and from the outpatient location and given instructions on where to go before and after HBO therapy. Similarly, for UK-MCC, patients will receive HBO therapy inpatient our outpatient using Sechrist Industries model 4100 located adjacent to the Emergency Department in the hospital. The HBO therapy will be monitored by a hyperbaric oxygen trained nurse. Following HBO therapy, all subjects will be admitted as inpatient and recommended to shower with chlorhexidine (CHG) soap, however, this is not required. The choice of these treatment parameters is based on our two recently conducted pilot studies indicating the safety and efficacy of these treatment paremeters.[18,37] In our pilot studies we chose standard HBO treatment conditions that have been adequately explored previously with good track record of safety and tolerance. Our pilot studies data showed that standard HBO conditions were safe in UCB transplant as well as in autologous HSPC transplantation setting. Additionally, the current treatment schedule did result in reducing erythropoietin levels significantly in both studies, which is the biologic marker of effectiveness of HBO therapy in improving engraftment in our studies. Since the use of HBO in hematopoietic stem cell transplant setting is novel, we will stagger enrollment for the first 5 patients randomized to the HBO arm. We plan to monitor the first 5 subjects receiving HBO for 30 days after HBO therapy prior to enrolling subsequent patients to the HBO arm. To minimize ear discomfort during HBO therapy, Bone Marrow Transplant medical providers should strongly encourage the use of supportive medications like over the counter nasal steroids if patients have signs of nasal allergies and/or cerumen removal kits for cerumen removal if they have wax upon ear exam at the time of

patient evaluation on Day -1 or Day 0 prior HBO therapy. Also, HBO staff might recommend these over the counter measures upon their independent evaluation. Also, sedatives like short acting benzodiazepines might be prescribed by the Bone Marrow Transplant medical providers for mild anxiety related to the procedure, which can be prescribed any time prior to Day -1. In the case of using sedatives prior to outpatient HBO therapy, the patient will be asked to arrange for someone else to drive to and from the Strong Wound Healing Center.

HSPC infusion:

All patients participating on this study should have peripherally mobilized and cryopreserved autologous HSPC products. Peripheral blood mobilization of autologous HSPCs is achieved by using high-dose G-CSF +/- plerixafor +/- high-dose cytoxan according to institutional guidelines. Autologous HSPCs are collected by apheresis. Between 6 and 10 hours following the start of HBO therapy, patients will receive Auto HSPC stored units. Auto HSPC dose should be ≥ $2x10^6$ CD34+cells/Kg body weight. Institutional standard operating procedures (SOPs) will be followed in terms of pre-medications and infusion. We cross reference IND 17373 for the pertinent Chemistry, Manufacturing, and Control (CMC) information.

4.3 Post-HBO assessment and monitoring:

A specific assessment for acute HBO toxicity will be collected within 24-hours of the procedure. The assessment is clinical and includes brief history and physical examination, including vitals.

Enrolled subjects will have daily blood counts checked after transplantation until ANC and ALC recovery is documented. Achieving an ALC of >500/mm^3 will be considered the day of ALC recovery. Additionally, ALC will be determined daily through day 15. Achieving ANC of >500/mm^3 for three consecutive days is considered day of ANC recovery. Blood counts will be checked daily until ANC recovery is documented, following that blood counts will be checked less frequently (2-3 times/week) until ANC, ALC, and platelet recovery are documented. Time to ANC recovery, ALC recovery, platelet recovery, number of PRBC and platelet transfusions, number of days of G-CSF use, and length of hospitalization will be determined for each patient, except patients who die prior to that, whose time to recovery measure will be right-censored at the date of death. In addition, we will collect the following information: CD34 cell dose and infused lymphocyte dose to determine using multivariate analysis if HBO effect on ALC recovery is independent of these factors that have been found to impact ALC recovery.

Patients will have disease assessment prior to and after transplant on day +100 and at 1 year using the International Response Criteria for multiple myeloma. Since maintenance therapy could potentially affect day +100 responses, it is recommended that maintenance therapy be held until after day +100 disease assessment is obtained.

4.4 Toxicities and Dosing Delays/Dose Modifications

Any subject who receives full or partial HBO treatment on this protocol will be evaluable for toxicity. Toxicity will be assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 4.03. Toxicities will be collected for up to 1-year post transplant. We will specifically assess for treatment-limiting toxicities (TLTs) defined as the occurrence of any of

the following complications within 24 hours of HBO: Seizure disorder, pneumothorax, death, any irreversible grade Ill or any grade IV toxicity.

4.5 Concomitant Medications/Treatments

No prohibited medications or treatments.

4.6 Duration of Therapy

- Unacceptable adverse event(s)
- Patient decides to withdraw from the study, **OR**
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator".

4.7 Duration of Follow Up

Patients will be followed for up to day +100 to assess disease response and at 1 year for PFS assessment. Patients continuing care at URMC will have disease status collected at the time of routine follow up appointments to determine progression free survival (PFS). All these visits are considered part of standard of care visits post-transplant. All CTCAE v4.03-defined adverse events of grades 1-5 will be recorded and reported to the sponsor, WCI CTO at each study visit. Events which are serious, unexpected and suspected adverse reactions to the experimental intervention should be reported expeditiously to FDA according to the timeframe noted in 21CFR312.32. All other AEs can be reported in aggregate in the annual report as described in 21CFR312.33(b)(1).

In the event that a patient decides to withdraw from the study treatment, we would like to continue to collect information from them for the duration of the study or (up to one year from the patient's transplant date). Patients do not have to agree to the continual optional data collection after withdrawal. Any follow-up data collected for this study will be for the purposes of monitoring adverse events that may occur as a result of the study or for changes related to disease progression.

4.8 Removal of Patients from Protocol Therapy

Subjects can choose to be removed from the protocol at any time.
Subjects will be removed from therapy when any of the criteria listed in Section 5.5 apply. Notify the Principal Investigator, and document the reason for study removal and the date the patient was removed in the Case Report Form. The patient should be followed-up per protocol.

4.9 REDCap for Study Database

After consent is obtained and screening procedures are complete, eligible subjects will be randomized within 4 weeks of planned study start. Each site will receive access to the studyspecific, REDCap database. Site users will enter subject demographic information directly into REDCap to receive an assignment in real time as eligible patients are registered. A URMC statistician will also have the randomization schema and will be able to communicate urgent randomization results to sites in case of REDCap login issues or system failures.

 Randomization Procedures: Study statisticians will prepare a 1:1 block randomization table based on random 4- and 6- blocks. This randomization table will be uploaded into the Randomization module in REDCap.

It is the expectation that all eligibility data has source documentation available at the enrolling sites. Site personnel will be responsible for entering subject data regularly into this database. REDCap will be used to accommodate data entry, data retrieval, and data security. Access to study data and proper back-up procedures will be utilized in REDCap.

4.10 Patient Replacement

Subjects who do not continue therapy on this protocol ***prior*** to HBO therapy will be replaced by new subjects.

5.0 STUDY PROCEDURES

5.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained. To help potential patients understand the clinical trial concept, we have prepared an animation that will be provided to prospective patients as a link on a handout and/or shown to potential subjects on a tablet or computer in clinic when time permits. The animation will be made available to potential subjects during the informed consent process and/or study screening

All screening procedures must be performed within 30 days prior to registration unless otherwise stated. The screening procedures include:

- **Informed Consent Medical history**
  - Complete medical, surgical and oncology history as well as history of infections are obtained at screening.
- **Demographics**
  - Demographic profile will include date of birth, gender, race, and zip code.
  - Baseline disease characteristics will be collected including the stage at diagnosis, cytogenetic and FISH anomalies, and the treatment medications used prior to ASCT
- **Review subject eligibility criteria** o Review of eligibility criteria as described in Section 3 to ensure subject qualification for study entry

- **Review previous and concomitant medications**
  - All prior medication taken by the subject within 7 days before starting the study is to be recorded. Concomitant medications taken by the subject during the study are to be recorded up until 30-days after last study dose. If a reportable adverse event (see Section 7) occurs within 30-days after last study dose, recording of concomitant medications should continue until resolution of the adverse event
- **Physical exam including vital signs, height and weight**
  - Vital signs (temperature, pulse, respirations, blood pressure), height, weight
- **Performance status**
  - Karnofsky Performance Status (KPS) will be evaluated at the time of physical exam prior to study entry and possibly during study. Specific criteria for assessing KPS can be found in Appendix A
- **Pregnancy test (for females of child bearing potential)**
  - See section 3.1 for definition
- **Hematology**
  - Hematology to include hemoglobin (Hgb), platelets, total white blood cell count (WBC) and differential
- **Serum chemistries**
  - Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT, AST, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin or BMP to include: BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose
- **EKG**
  - EKG within 60 days of the anticipated transplant date, unless clinically indicated
- **Chest x-ray**
  - Chest x-ray within 60 days of the anticipated transplant date, unless clinically indicated

- **MUGA or ECHO**
  - 2D-ECHO or MUGA scan within 90 days of the anticipated transplant date, unless clinically indicated
- **Disease assessment**
  - For multiple myeloma, the **International Response Criteria** for **multiple myeloma** will be applied.[38]
- **Pulmonary Function Test**
  - PFT to be performed within 90 days of the anticipated transplant date, unless clinically indicated

Procedures During Treatment

- **Day -1**
  - Chemotherapy preparative regimens as outlined in Section 4.0.
  - Blood draw for correlative studies prior to chemotherapy administration.
  - Physical exam and vital signs
- **Day 0, pre-HBO**
  - CBC
  - Blood draw for correlative studies
  - Physical exam and vital signs
- **Day 0**
  - HBO treatment
- **Day 0, at least 6 hrs, but no more than 10 hours post-HBO**
  - HSPC unit transplantation
  - Blood draw for correlative studies just prior to HSPC infusion and two hours later.
- **Day 1**
  - Physical exam
  - Vital signs
  - CBC

- Acute HBO toxicity assessment
  - Blood draw for correlative studies

- **Days 1 – 14 Every Day Post-Transplant** ○ CBC with diff (daily until neutrophil recovery)
  - Correlative lab draws (day 2, 3, and 7 post-transplant, and on first day of neutrophil recovery). A window of 3 hours is allowed. If day 7 time point or first day of neutrophil recovery sample occurs on a weekend or a holiday, the sample is to be collected the first business day after the weekend or holiday. ○ Physical exam and vital signs
  - G-CSF 5 mcg/kg will be given daily subcutaneously, until ANC≥500 for three consecutive days or ANC≥1500 for one day

- **Day 15 post-transplant (2 day window allowed)** ○ Blood draw for CBC with diff and correlative studies. A window of two days is allowed for correlative studies. If any of these days occur on a weekend or a holiday, the correlative study sample is to be collected the first business day after the weekend or holiday
  - Physical exam and vital signs ○ Study survey to evaluate patient's HBO experience.

- **Day 100 post-transplant** ○ CBC with diff ○ Disease Assessment per standard criteria.
  - Blood draw for correlative studies within a 2 week window is allowed to accommodate any scheduling issues. ○ Physical exam and vital signs

- **1- year post-transplant** (1 month window is allowed to accommodate any scheduling issues) ○ Disease Assessment per standard criteria ○ Physical exam and vital signs

5.2 Follow-up Procedures

Patients will be seen daily on the inpatient ward until neutrophil count recovery, then if their condition allows will be discharged to outpatient with visits scheduled 2-3 times a week for the first 30 days as clinically indicated. Laboratory testing will occur per institutional guidelines. Neutrophil recovery is defined as ANC ≥ 500/μL for three consecutive days. Follow up for AEs or SAEs will begin from the start of treatment at Day -1 and will continue until day +100 post-transplant. All CTCAE v4.03-defined adverse events of grades 1-5 will be recorded and reported to the sponsor at each study visit. Events which are serious, unexpected and suspected adverse reactions to the experimental conditions, i.e: HBO, should be reported expeditiously to FDA according to the timeframe noted in 21CFR312.32. All other AEs can be reported in aggregate in the annual report as described in 21CFR312.33(b)(1).

5.3 Schedule of Events

HBO+AutoHSPC STUDY CALENDAR	Screening/ Baseline	Day -1	Day 0, pre-HBO	Day 0 HBO	6 hrs Post HBO	8 hrs Post HBO	Day 1 (24 hrs post HBO)	Day 2 and 3 (post HBO)	Every Day - Days 1-14 Each Day PostTransplant
Approximate Visit Time									
Informed Consent	X								
Medical History	X								
Concomitant Medication	At each clinical encounter								
Physical Exam (With performance status)	At each clinical encounter								
Adverse Events		At each clinical encounter							
Pregnancy Test	X								
CBC with diff	X		X				X	X	X
MUGA or ECHO	X								
Pulmonary Function Tests	X								
Disease Assessment	X								
High-dose melphalan (Preparative Regimen)		X							
Correlative Blood Samples (EPO, IL-15)		X	X		X	X	X	X	
HBO Treatment				X					
HSPC Transplant					X				
Acute HBO Toxicity Assessment							X		
Growth factor use days									X

HBO+AutoHSPC Study Calendar - CONTINUED

HBO+AutoHSPC Study Calendar	Day 7 Post-Transplant	First day of neutrophil recovery (+/- 2 days)	Day 15 Post – Transplant (+/- 2 days)	Day 100 Post Transplant	Long-term follow up for PFS 1 year post-transplant
Medical History	Each clinical encounter				
Concomitant Medication	Each clinical encounter				
Physical Exam (with performance status)	Each clinical encounter				
Vital Signs	Each clinical encounter				
Adverse Events	Each clinical encounter				
Disease Assessment				X	X
Research Blood Samples (CBC with diff for ALC Recovery)			X		
Correlative Blood Samples (IL-15, NK cells, EPO)	X**	X**	X	X***	
Study survey			X****		
Duration of hospitalization And readmissions	Data will be collected through day +100				
Blood product transfusions	Data will be collected through day +100				

* A window of 3 hours is allowed for post-transplant day 1, 2, and 3 sample collection. If day 7, day 15 or first day of neutrophil recovery sample collection days occur on a weekend or a holiday, the sample is to be collected the first business day after the weekend or holiday.

** On day 7 and first day of neutrophil recovery patients will have blood drawn for IL-15 and EPO.

*** On day 100 patients will have blood drawn for IL-15.

**** To be completed by patients who completed HBO therapy.

5.4 Removal of Subjects from Study Treatment and Study

Subject can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

5.4.1 Subject voluntarily withdraws from treatment (follow-up permitted);

5.4.2 Subject withdraws consent (termination of treatment and follow-up);

5.4.3 Subject is unable to comply with protocol requirements;

5.4.4 Subject experiences toxicity that makes continuation in the protocol unsafe;

5.4.5 Treating physician judges continuation on the study would not be in the subject's best interest;

5.4.6 Subject becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);

5.4.7 Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study; **5.4.8** Lost to follow-up.

6.0 ADVERSE EVENTS

Text below in italics is verbatim from "Guidance for Industry and Investigators. Safety Reporting Requirements for INDs and BA/BE Studies", issued December 2012 by U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, and Center for Biologics Evaluation and Research. The guidance may be retrieved from:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf?source=govdelivery.

Potential Risk: The potential risks associated with this study are considered minimal and consist of those related to phlebotomy (i.e. rare local infection or rare local bleeding necessitating temporary pressure dressing) and possible reactions and adverse events related to hyperbaric oxygen (HBO). The more common and less serious complications related to HBO include middle ear barotrauma, which occurs at incidence of 13.6% as described in one study. On the other hand, seizures have been reported to occur at a rate of.033% in one report, or 1.3 in 10,000 in another report. The benefits from this research potentially outweigh these small risks. Based on our pilot study findings, this procedure was well-tolerated.

Procedures to Minimize Potential Risks: Blood samples for study purposes will be obtained by an experienced health care professional using standard aseptic techniques. Local pressure will be applied at the site of phlebotomy to minimize bleeding or bruising. All results obtained from laboratory tests will be provided to the participants upon request. The data collected will be used for research purposes only, and participants will be identified by study IDs. To minimize risks related to HBO therapy, we will exclude patients who have a history of claustrophobia,

spontaneous pneumothorax, history of seizures, and sinus surgery five years prior to enrollment.The treatment will be stopped immediately, temporarily or permanently, in the event the treated subject develops any acute complications, or upon his/her request. Standard operating procedures will be followed in case of development of acute complication during therapy.

Monitoring for All Risks: All risks have been minimized to the greatest extent possible for this study as a prior pilot study indicated the safety of HBO in this setting. URMC, KUMC, or UK-MCC will not assume responsibility for any costs related to potential injury from this study, again we do not anticipate any injury. If an injury does occur, subjects will be asked to notify the PI immediately, and notify the bone marrow transplant providers. All data obtained from subjects will remain confidential and be securely maintained by the Clinical Trials Office at each institution. All electronic data will be password protected.

6.1 Definitions

6.1.1 Adverse Event [21 CFR 312.32(a)]

An adverse event means any untoward medical occurrence associated with the use of a drug or an intervention in humans, whether or not considered drug related.

An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

This study will use the descriptions and grading scales from Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v 4.03) for hematologic and non-hematologic toxicities. Detailed information may be found on the Cancer Therapy Evaluation Program (CTEP) website: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All CTCAE v4.03defined adverse events of grades 1-5 will be recorded and reported to the sponsor at each study visit. Events which are serious, unexpected and suspected adverse reactions to the experimental biologic should be reported expeditiously to FDA according to the timeframe noted in 21CFR312.32. All other AEs can be reported in aggregate in the annual report as described in 21CFR312.33(b)(1).

Information for adverse events, whether reported by the subject, directly observed, or detected by physical examination, laboratory test or other means, will be collected, recorded, followed and reported in the CRF as described in the following sections.

Adverse events experienced by subjects will be collected and reported from time of treatment start on Day -1, throughout the study, and within 100 days of the last treatment of protocol therapy. Subjects who experience an ongoing adverse event related to a study procedure and/or study treatment beyond 100 days will continue to be contacted by a member of the study team until the event is resolved, stabilized, or determined to be irreversible by the principal investigator. Study subjects should also be instructed to report any new serious post-study event(s) that might reasonably be related to participation in this study.

Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, or require therapy. In this case they will be recorded on the Adverse Events CRF, along with the associated signs, symptoms or diagnosis.
As far as possible, each adverse event will also be described by:

- its duration (start and end dates),
- grading of severity,
- its relationship to the study drug,
- the action(s) taken,
- outcome

6.1.2 Suspected Adverse Reaction [21 CFR 312.32(a)]

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug or intervention caused the adverse event. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug/intervention and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Suspected adverse reactions are the subset of all adverse events for which there is a reasonable possibility that the drug/intervention caused the event. Inherent in this definition, and in the requirement to report suspected adverse reactions, is the need for the sponsor to evaluate the available evidence and make a judgment about the likelihood that the drug/intervention actually caused the adverse event.

Factors to be considered in assessing the relationship of the adverse event to study treatment include:

- The temporal sequence from study treatment administration: The event should occur after the study treatment is given. The length of time from study treatment exposure to event should be evaluated in the clinical context of the event.
- Recovery on discontinuation (de-challenge): Subject's response after treatment discontinuation (de-challenge) should be considered in the view of the usual clinical course of the event in question.
- Underlying, concomitant, intercurrent diseases: Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant medication or treatment: The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them may be suspected to cause the event in question.

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- Unrelated - The AE is clearly **NOT** related to the study treatment. Unlikely - The AE is **doubtfully related** to the study treatment.
- Possible – The AE **may be related** to the study treatment. Probable – The AE is **likely related** to the study treatment.
- Definite – The AE is **clearly related** to the study treatment.

6.1.3 Unexpected [21 CFR 312.32(a)]

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application… "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs/intervention or as anticipated from the pharmacological properties of the drug/intervention, but are not specifically mentioned as occurring with the Particular drug/intervention under investigation.

This definition relies entirely on a listing of the adverse events or suspected adverse reactions in the investigator brochure…as the basis for determining whether newly acquired information generated from clinical trials or reported from other sources is unexpected. This means that events not listed for the Particular drug under investigation in the investigator brochure are considered "unexpected" and those listed are considered "expected." When new adverse event information is received, it is the sponsor's responsibility to determine whether the event is "unexpected" for safety reporting purposes.

6.1.4 Serious [21 CFR 312.32(a)]

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be lifethreatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

6.1.5 Life-threatening

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or patient at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

6.2 Reporting Requirements for Adverse Events

6.2.1 Submitting Serious Adverse Events Reports to IRB

For serious adverse events, the clinical research site will follow local IRB policies and procedures.

6.2.2 Study Investigator Notification of Adverse Events

All **expected** and **unexpected** serious adverse events occurring after the subject has signed the Informed Consent and has started protocol treatment must be reported to the study principal investigator within 24 hours of becoming aware of the event:

PI Name: Omar Aljitawi, MD
Office Phone: 585-276-6259
Fax: 585-276-2596

6.2.3 DSMC Notification of SAEs

See Section 10.0

6.2.4 Recording Adverse Events and Documentation in WCI Clinical Trials REDCap database

All **expected** and **unexpected** adverse events and serious adverse events occurring after the subject has signed the Informed Consent and has started protocol treatment must be fully recorded in the subject's case record form.

All unexpected SAEs should be reported in the REDCap database within 5 business days of learning of the event, while other SAEs should be reported bi-annually to DSMC. SAE reports are expected to include sufficient detail so that the WCI DSMB can determine the severity, toxicity grade, expectedness and treatment. The report should be updated to document resolution or any sequelae. The Coordinating Center, WCI, will report an aggregate listing of all AEs and SAEs for review at the regular DSMB meetings. The board will review these reports and determine if further action is required. SAEs that are determined to be related to study intervention AND unexpected require expedited reporting to the REDCap database in addition to notification by email to study PI.

The Coordinating Center will report these events to the WCI DSMB in addition to sending a formal notification describing the event to all investigators. Each investigator must then notify his or her IRB of the event according to local regulations.

Documentation must be supported by an entry in the subject's file. A laboratory test abnormality considered clinically relevant, e.g., causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator, should be reported as an adverse event. Each event should be described in detail along with start and stop dates, severity, relationship to investigational product, action taken and outcome.

6.2.5 Reporting of Unexpected, Related SAEs for Hyperbaric Oxygen (HBO)

For HBO, all unexpected, related serious adverse experiences will be forwarded to the product manufacturer by the investigator using the Voluntary MEDWATCH Form FDA 3500.

6.2.6 Summary of Expedited Serious Adverse Event Reporting

	Relationship to study investigational therapy	**WCI Clinical Trials DSMC**	**IRB**	**PI**
Unexpected SAE	Related	5 days	5 days	24 hrs
Unexpected SAE	Not-related	Bi-Annual meeting	Not reportable	24 hrs
Expected SAE	Related	Bi-Annual meeting	Not reportable	24 hrs
Expected SAE	Not-related	Bi-Annual meeting	Not reportable	24 hrs

7.0 DRUG INFORMATION

7.1 Hyperbaric oxygen

- Agent Classification: Physiologic agent

- Mode of action: Investigators think that HBO alters the recipients' microenvironment to facilitate engraftment of hematopoietic stem and progenitor cells.

- Route of administration for this study: Via monoplace hyperbaric chamber (Model 3300H, Sechrist Industries, Inc., USA). The treatment will be given at the Strong Wound Healing Center; University of Rochester, Rochester, NY 14620. At KUMC, the treatment will be given via Sechrist Industries model 3200/3200R at the Hyperbaric Medicine unit at KUMC. At UKMCC, the treatment will be given Sechrist Industries model 4100 located adjacent to the Emergency Department in the hospital.

- Availability: This is an FDA approved therapy for several indications.

  Side effects: Administration of HBO is generally considered a safe procedure when standard protocols are used. This includes oxygen pressures not exceeding 3 atmospheres and treatment sessions limited to a maximum of 120 minutes.[46] Adverse events, however, can occur. The most common complication is reversible myopia. Cataract formation using standard procedures is usually not seen.[46] Cavity trauma secondary to pressure change (i.e., sinus trauma or tympanic membrane rupture) has also been observed.[47] These complications can be minimized by adhering to standard procedures and patient education.[48] An example of a rare but serious complication is pneumothorax, which usually occurs in patients with severe lung disease.[47] Seizures have been reported to occur at a rate of 1.3 seizures per 10,000 treatments, but are reversible by reducing the pressure of inspired oxygen.[48] HBO therapy is considered an effective therapy for decompression sickness and air embolism.[47] Other indications include carbon monoxide poisoning,[49] treatment of infections such as gas gangrene, necrotizing fasciitis, diabetic foot infections, refractory osteomyelitis, neurosurgical infections and fungal infections.[50]

8.0 CORRELATIVES/SPECIAL STUDIES

The goal of the planned laboratory correlative studies is to investigate potential mechanisms by which hyperbaric oxygen improves time to ANC, ALC, and platelet recovery, days of G-CSF use, PRBC/platelet unit utilization, and length of hospital stay. These correlative studies investigate the effect of hyperbaric oxygen on EPO and IL-15 in response to HBO following transplant and correlate that with time to ANC, ALC, and platelet recovery, days of G-CSF use, PRBC/platelet unit utilization, and length of hospital stay.

Sample Collection Guidelines:
Peripheral blood samples will be collected by drawing blood from central venous catheters or peripheral vein. Samples will be labeled with the subject's de-identified study number and collection date and processed for plasma/serum isolation and storage by CTO.

CTO
WCI, second floor
University of Rochester Medical Center

Samples will be collected at the following time points (+/- 3 hour window): prior to initiation of preparative regimen (day-1), prior to HBO treatment on day 0, and following HBO therapy (6 hrs and 8 hrs from start of HBO and days 1, 2, and 3 after starting HBO). Additional sample will be collected on the first day of neutrophil recovery, day +15, and day +100. Samples will be collected from controls at the same time points. Blood samples collected at KUMC or UK-MCC will be processed, stored, and shipped to URMC for storage and for testing by the corresponding Biospecimen Repository Core Facility (BRCF). All correlative study testing will occur at URMC.

8.1 Assay Methodology

Enzyme-linked immunosorbent assay (ELISA) will be used to measure EPO and IL-15 in plasma/serum samples from enrolled subjects. Flow cytometry will be done to document NK cell recovery.

8.2 Specimen Banking

Submission of samples for the correlative studies is mandatory for this study. Subject samples collected for this study will be retained by CTO at WCI. Specimens will be stored indefinitely or until they are used up.

With the subject's permission, any leftover specimens will be stored and used for future research studies by the PI or other investigators at URMC for IRB approved research purposes if approved by the PI. If the leftover specimen samples for storage and future use is denied or withdrawn by the subject (submitted in writing to the investigator), best efforts will be made to stop any additional studies and to destroy the specimens.

9.0 MEASUREMENT OF EFFECT

9.1 Safety / Tolerability

Analyses will be performed for all subjects having received the full or partial hyperbaric oxygen treatment for any duration. The study will use the CTCAE version 4.03 (http://ctep.cancer.gov/reporting/ctc.html) for reporting of hematologic and non-hematologic adverse events.

10.0 DATA AND SAFETY MONITORING

10.1 Oversight and Monitoring Plan

Study Investigators at each institution will conduct continuous review of data and patient safety. The Principal Investigator (PI) at each institution will submit bi-annual progress reports of these data to the Data Safety Monitoring Committee at the corresponding institution for review. The review will include for each treatment arm: the number of patients enrolled, withdrawals, significant toxicities as described in the protocol, serious adverse events both expected and unexpected, dose adjustments, and responses observed. The PI at each institution maintains a database of all adverse events with toxicity grade and information regarding treatment required, complications, or sequelae. The PI at each institution will submit a copy of the AE spreadsheet along with a Progress Report to the Data Safety Monitoring Committee (DSMC) at WCI for review. Actual review dates will be assigned when the 1st patient is accrued.

The DSMC at the Wilmot Cancer Institute of the University of Rochester provides oversight of study progress and safety by review of accrual and adverse events at bi-annual meetings or more often if concerns arise. Any adverse event requiting expedited review per protocol, including those occurring at participating sites, will be submitted to the Safety Coordinator of the DSMC at WCI for determination as to whether further action is required. When patient safety is of concern, an interim meeting may be called in any of the following situations:

- Any serious adverse event that is serious, related AND unexpected must be reported within 5 calendar days to both the WCI DSMC Safety Coordinator and the local IRB (see institutional IRB guidelines). The WCI DSMC Chair will determine whether further action is required, and when patient safety is of concern.
- Serious adverse events that are related AND expected or unrelated AND unexpected will be reported to the WCI DSMC for review at the bi-annual meeting. SAE reports are expected to include sufficient detail so that the WCI DSMC can determine the severity, toxicity grade, expectedness, treatment required, and a follow up report documenting resolution or if there are sequelae. Serious adverse events that require detailed reports (but not necessarily expedited) are expected, related, non-hematologic toxicities of grades 3, 4 or 5.

The Safety Coordinator administratively coordinates reports and data collection and prepares documents for the WCI DSMC Chair and committee review. The Safety Coordinator will administratively monitor adverse event rates utilizing the report from the study database. If any study has had two or more of the same SAE's reported in a month or more than six of the same SAE's in six months, the WCI DSMC will review the summary of SAEs, discuss events with Study Chair, and conduct a more detailed review with the Study Chair. The Data Safety Monitoring Chair will determine if further action is required.

10.2 Stopping Rules

The study activities will be monitored by the **Data and Safety Monitoring committee (DSMC) at WCI. Also, SAE and suspected but unexpected SAE will be reported to the FDA according to FDA guidance (2012) and 21 CFR312.32. Any death should be evaluated in the context of expected autologous transplant mortality to determine the relationship to HBO.**

11.0 REGULATORY CONSIDERATIONS

11.1 Protocol Review and Amendments

This protocol, the proposed Informed Consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the local IRB prior to implementation. Any changes in study conduct must be reported to each IRB. The Principal Investigator will disseminate protocol amendment information to all participating investigators. All decisions of the IRB concerning the conduct of the study must be made in writing.

11.2 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

11.3 Ethics and Good Clinical Practice (GCP)

This study is to be conducted according to the following considerations, which represent good and sound research practice:

1. ICH Consolidated Good Clinical Practice: Guidelines (E6) www.fda.gov/cder/guidance/iche6.htm
2. US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki
   - Title 21 Part 11 – Electronic Records; Electronic Signatures www.access.gpo.gov/nara/cfr/waisidx_02/21cfr11_02.html
   - Title 21 Part 50 – Protection of Human Patients www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html
   - Title 21 Part 54 – Financial Disclosure by Clinical Investigators www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html
   - Title 21 Part 56 – Institutional Review Boards www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html
   - Title 21 Part 312 – Investigational New Drug Application www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html
3. State laws
4. Institutional research policies and procedures

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the institutional IRB according to the local reporting policy.

12.0 REGISTRATION PROCEDURES

12.1 General Guidelines for URMC and Other Participating Organization

Participating institutions will register eligible subjects through the WCI Clinical Trials Office central registration process. Registration must occur prior to the initiation of therapy, with treatment assignment provided by WCI. Any subject not registered to the protocol before treatment begins will be considered ineligible and registration will be denied. Subjects should be registered within 5 working days prior to starting treatment.

The completed source documentation provided for eligibility verification and registration must be kept in the subject binder for monitoring purposes and documentation of subject eligibility.

Issues that would cause treatment delays should be discussed with the Principal Investigator. If a subject does not receive protocol therapy following registration, notify the WCI BMT/Myeloma Team so that the subject's status can be changed in REDCap.

12.2 Registration Process for URCC and Other Participating Centers

All ethical, regulatory, technical, and scientific approvals must be in place before study registrations will be accepted from a site.

All subjects will be registered centrally through the coordinating site Clinical Trials Office which is located at the:

James P. Wilmot Cancer Institute
University of Rochester Medical Center
Rochester, NY 14642

The Coordinating Center functions both as a Participating Center and as the Coordinating Center.

Each site will receive access to the study-specific, REDCap database at the University of Rochester. It is the expectation that all data has source documentation available at the enrolling sites. Site personnel will be responsible for entering their patient data regularly into this database.

At the time of registration, the signed informed consent form and documents that support eligibility should be faxed to the Coordinating Center: 585-442-0137, Attn: BMT/Myeloma Team.

Any question regarding eligibility or that may arise during the conduct of the study should be addressed to:

Name: Omar Aljitawi, MBBS
Email: omar_aljitawi@urmc.rochester.edu
Phone: 585-273-3258

13.0 STUDY MANAGEMENT

13.1 Overall Study Organization

For this study, the WCI CTO is considered the Sponsor, the Coordinating Site, and one of the sites for study activities. KUCC is considered the second site.

13.2 Investigator Files and Retention of Documents

Each site investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified. Original source documents supporting entries in the case report forms include but are not limited to hospital records and clinic charts, laboratory and pharmacy records, ECG, signed ICFs, subject diaries and pathology reports. All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

13.3 Case Report Forms

Case report forms (CRFs) will be completed for each subject enrolled. All CRFs will be complete and accurate. The medical chart and any other clinical worksheets, procedural reports, etc. are the source of verification of the data captured into the study database by each participating institution.

13.4 Study Monitoring

The study will be monitored by the coordinating center at yearly intervals to assure compliance to GCP and to assess the data quality and study integrity.

The investigator and staff are expected to cooperate and provide all relevant study documentation in detail at each site visit on request for review. The study monitors provided by WCI CTO will have direct access to source data for data verification. Data verification will be conducted by comparing the data entered into the CRFs with source data. Also, unexpected SAEs and unexpected suspected SAEs will be reported to the FDA according to FDA guidance (2012) and 21 CFR312.32. Any death should be evaluated in the context of expected UCB mortality to determine the relationship to HBO.

14.0 STATISTICAL CONSIDERATIONS

14.1 Study Design/Study Endpoints: 1:1 randomized clinical trial. The primary endpoint of the study is time from transplant to neutrophil recovery. Secondary endpoints will include time to platelet recovery, time to absolute lymphocyte count recovery, days of G-CSF use, PRBC units received, platelet units received, length of hospital stay, disease response at 100 days post-transplant and PFS at 1 year.

Primary Objective Statistical considerations: The primary endpoint of the study is time from transplant to neutrophil recovery. We expect no loss to follow-up or death prior to neutrophil recovery, and expect to observe neutrophil recoveries in all patients. Our assumptions are based largely on a recent single-arm study of hyperbaric oxygen in ASCT (REF). We hypothesize that HBO will increase the relative hazard of neutrophil recovery by 80%, corresponding to a hazard ratio (HR) of 1.8. This corresponds with a decrease in proportion who have not had a neutrophil recovery at 10 days from 81% to 68%, or alternatively, an increase in 10 day neutrophil recovery from 19% to 32%. 100 subjects (50 per arm) provides 81% power to detect HR=1.8 at a two-sided α=0.05 level

of significance. Subjects will be 1:1 block-randomized, with random block sizes of 4 and 6. The primary analysis will be stratified by quartiles of the actual infused cell dose (each stratum will include 25% of the enrolled subjects).The primary analysis will be a 1-degree of freedom (1-df) likelihood ratio test (LRT) of HBO treatment in the cell dosestratified Cox model. As we expect many ties in recovery time, the exact method will be used to handle ties in the Cox model. The HR for HBO will be reported along with a 95% confidence interval (CI) and associated LRT p-value. Time to neutrophil recovery by HBO group will be summarized graphically via the Kaplan-Meier method.

Secondary Objective: Statistical Considerations: Secondary endpoints will include time to platelet recovery, time to absolute lymphocyte count recovery, days of G-CSF use, PRBC units received, platelet units received, length of hospital stay, disease response at 100 days post-transplant and PFS at 1 year. Time to event outcomes will be analyzed using methods detailed above. Continuous outcomes will be compared between groups using the non-parametric Wilcoxon rank-sum test, and binary outcomes will be compared using Fisher's exact test.

Exploratory Objective Statistical Considerations: To explore HBO effects on IL-15 and EPO responses and NK cell recovery, we will use a linear mixed model (and model diagnostics described above for assessment) with treatment group as the explanatory measure of interest

14.2 Sample Size and Accrual

Primary Objective Sample size justification: The primary endpoint of the study is time from transplant to neutrophil recovery. We hypothesize that HBO will increase the relative hazard of neutrophil recovery by 80%, corresponding to a hazard ratio (HR) of 1.8. This corresponds with a decrease in proportion who have not had a neutrophil recovery at 10 days from 81% to 68%, or alternatively, an increase in 10 day neutrophil recovery from 19% to 32%. 100 subjects (50 per arm) provides 81% power to detect HR=1.8 at a two-sided α=0.05 level of significance.

14.3 Data Analyses Plans

Objective 1: Final analysis will be done after all patients are enrolled and completed 1-year of follow up.

15.0 REFERENCES

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16.0 APPENDICES

Appendix A. Performance Status

KARNOFSKY PERFORMANCE STATUS SCALE
DEFINITIONS RATING (%) CRITERIA

Able to carry on normal activity and to work; No special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; Minor signs or symptoms of disease.
	80	Normal activity with efforts; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; Requires equivalent of institutional or hospital care; diseases may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; Active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

Oxford Textbook of Palliative Medicine, Oxford University Press. 1993;109.

FUNCTIONAL ASSESSMENT STAGING (FAST)
(Check highest consecutive level of disability.)

1. No difficulty either subjectively or objectively.
2. Complains of forgetting location of objects. Subjective work difficulties.
3. Decreased job functioning evident to co-workers. Difficulty in traveling to new locations. Decreased organizational capacity. *
4. Decreased ability to perform complex task, (e.g., planning dinner for guests, handling personal finances, such as forgetting to pay bills, difficulty marketing, etc.)
5. Requires assistance in choosing proper clothing to wear for the day, season or occasion, (e.g. patient may wear the same clothing repeatedly, unless supervised. *)
6. A) Improperly putting on clothes without assistance or cueing (e.g., may put street clothes on over night cloths, or put shoes on wrong feet, or have difficulty buttoning clothing) (Occasionally or more frequently over the past weeks. *)
   B) Unable to bathe properly (e.g., difficulty adjusting bath-water temperature) (Occasionally or more frequently over the past weeks. *)
   C) Inability to handle mechanics of toileting (e.g., forget to flush the toilet, does not wipe properly or properly dispose of toilet tissue) (Occasionally or more frequently over the past weeks. *)
   D) Urinary incontinence (Occasionally or more frequently over the past weeks. *)
   E) Fecal incontinence (Occasionally or more frequently over the past weeks. *)
7. A) Ability to speak limited to approximately a half a dozen intelligible different words or fewer, in the course of an average day or in the course of an intensive interview.
   B) Speech ability is limited to the use of a single intelligible word in an average day or in the course of an intensive interview (the person may repeat the word over and over.)
   C) Ambulatory ability is lost (cannot walk without personal assistance.)
   D) Cannot sit up without assistance (e.g., the individual will fall over if there are not lateral rests [arms] on the chair.)
   E) Loss of ability to smile.
   F) Loss of ability to hold up head independently.

*Scored primarily on the basis of information obtained from acknowledgeable informant and/or category.
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Appendix B. Stopping Rules High-dose therapy and Auto-HSPC is a well-tolerated procedure with low mortality (<5%) typically related to infections, hemorrhage, or organ toxicities from chemotherapy including interstitial pneumonitis and veno-occlusive disease of the liver.[39] Any death will be evaluated in the context of expected Auto-HSPC mortality to determine the relationship to HBO. In the event of death within 30 days of study treatment, accrual to study will pause pending assessment of the risk. For stopping rules, if HBO patients develop grade III or IV TLTs or demonstrate disease progression/relapse at day +100 in 20% or higher frequency than the standard arm, accrual to study will be halted until full evaluation by the WCI DSMC.

Appendix C. Study Survey

Subjects who complete HBO therapy will be asked to complete a quick 5 minute survey (see below) regarding their HBO experience on day +15 post-transplant. The study team will analyze the data in the future to help understand patient's experience with HBO in HSPC transplantation setting.

Direction: Check the box that best corresponds to your answer. Use the legend as your guide.

LEGEND: 5-Stongly Agree 4-Agree 3-Neither 2-Disagree 1-Strongly Disagree

Question	5	4	3	2	1
I had a good understanding of the hyperbaric oxygen study and its' purpose at the time of study consent.					
The visual slides and the informational packet helped me understand the study procedures.					
The assessment appointment at the Strong Wound Clinic helped prepare me for my hyperbaric oxygen therapy-treatment.					
The Strong Wound Clinic was easily accessible for my hyperbaric oxygen treatment					
The wound clinic staff were very helpful in delivering hyperbaric oxygen therapy					
Participating in the study made the transplant process more overwhelming.					
Scheduling/coordinating study related visits was simple.					
Overall, I feel that hyperbaric oxygen therapy assisted in my recovery.					
I am satisfied with my overall study experience.					

Comments/Suggestions:

Subject ID: …….. Date:……..
Initials:……