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Autologous

# Results of the First Clinical Study in Humans That Combines Hyperbaric Oxygen Pretreatment with Autologous Peripheral Blood Stem Cell Transplantation

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A B S T R A C T

Patients undergoing high-dose chemotherapy and autologous hematopoietic cell transplantation (auto-HCT) are at risk for multiple morbidities, including mucosal inflammation and neutropenic fever, both related to neutropenia. Evidence from our preclinical work in an umbilical cord blood (UCB) transplantation murine model suggests that treatment with hyperbaric oxygen (HBO) before UCB infusion improves UCB $CD34^+$ cell engraftment by reducing erythropoietin levels. A pilot clinical trial using HBO in patients undergoing UCB transplantation showed improvement in kinetics of blood count recovery. In this study, we evaluated HBO in combination with auto-HCT. Our primary aim was to determine the safety of HBO in this setting and secondarily to determine its efficacy in reducing time to neutrophil and platelet engraftment compared with matched historic controls. Patients with multiple myeloma, non-Hodgkin lymphoma, and Hodgkin disease eligible for auto-HCT were included. On day 0, patients received HBO treatment consisting of exposure to 2.5 atmosphere absolutes for a total of 90 minutes, in a monoplace hyperbaric chamber, breathing 100% oxygen. Six hours after the start of HBO, peripherally mobilized stem/progenitor cells were infused and patients were followed daily for toxicity and blood count recovery. All patients received daily granulocyte colony-stimulating factor starting on day +5 and until absolute neutrophil count (ANC) of $\geq$1500 or ANC of 500 for 3 consecutive days. A matched historic cohort of 225 patients who received auto-HCT between January 2008 and December 2012 was chosen for comparison and matched on sex, age, conditioning regimen, and disease type. We screened 26 patients for this study; 20 were treated and included in the primary analysis, and 19 completed the HBO therapy and were included in the secondary analysis. Although the median time to neutrophil count recovery was 11 days in both the HBO and control cohorts, the Kaplan-Meier estimates of the full distributions indicate that the time to neutrophil recovery was generally about 1 day sooner for HBO versus historical controls (log-rank $P = .005$; range, 9 to 13 for HBO patients and 7 to 18 for controls). The median time to platelet count recovery was 16 days (range, 14 to 21) for HBO versus 18 days (range, 11 to 86) for controls (log-rank $P < .0001$). In the secondary analysis comparing the HBO cohort who completed HBO therapy (n = 19) with our historical cohort, we evaluated neutropenic fever, growth factor use, mucositis, day +100 disease responses, and blood product use. HBO was associated with less growth factor use (median 6 days in HBO cohort versus median 8 days in controls, $P < .0001$). Packed RBC and platelet transfusion requirements were not statistically different between the 2 cohorts. Mucositis incidence was significantly lower in the HBO cohort (26.3% in HBO cohort versus 64.2% in controls, $P = .002$). HBO therapy appears to be well tolerated in the setting of high-dose therapy and auto-HCT. Prospective studies are needed to confirm potential benefits of HBO with respect to earlier blood count recovery, reduced mucositis, and growth factor use, and a cost-benefit analysis is warranted.


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## INTRODUCTION

Autologous hematopoietic cell transplantation (auto-HCT) following high-dose chemotherapy has an important role in treating many patients with lymphoma and multiple myeloma. For patients with a variety of lymphomas, including Hodgkin disease (HD) and non-Hodgkin lymphoma (NHL), auto-HCT might potentially be a curative procedure, in addition to improving overall survival and progression-free survival [1–5]. For multiple myeloma, auto-HCT is not curative, but its role is well established as a consolidation treatment to achieve deep durable remissions in most patients [6–9].

However, multiple adverse events may develop during or after auto-HCT related to the high-dose chemotherapy. Many patients have significant immediate transplant-related morbidities, including pancytopenia, that require transfusions of blood products and granulocyte colony-stimulating factor (G-CSF) support, as well as mucositis and infectious complications [10,11]. Neutropenia and subsequent infections remain the most common cause of early mortality [12–14]. Studies have showed that G-CSF support may improve neutrophil recovery and decrease the incidence of infections [15,16]. Mucositis incidence and severity are also related to prolonged neutropenia [17,18]. Hemorrhagic complications secondary to thrombocytopenia require platelet transfusions [19–21], which adds to the total cost of transplants: the average 60-day platelet transfusion cost per patient undergoing auto-HCT was estimated to be around $4000 [22]. Given the impact of the transplant-related mortality and morbidity, innovative modalities are needed to reduce the incidence of these serious complications and potentially reduce days of hospitalization, transfusion requirements, antibiotic use, and narcotic use for mucositis, any of which might reduce the overall cost of auto-HCT.

Previously, we have demonstrated that erythropoietin (EPO) plays a role in umbilical cord blood (UCB) hematopoietic stem/progenitor cell (HSPC) homing and engraftment, as EPO exposure impairs UCB HSPC in vitro transmigration [23,24]. Recognizing the negative effects of EPO on HSPC homing in UCB transplantation, we investigated hyperbaric conditions as an intervention to lower EPO in transplant recipients to improve HSPC homing, given that hyperbaric oxygen (HBO) is known to reduce EPO in healthy volunteers [25]. 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 [24]. We also evaluated the impact of HBO on UCB $CD34^+$ cell engraftment in a murine transplant model. In these experiments, irradiated mice that received HBO treatment before UCB cell infusion showed significantly improved myeloid, B cell, and T cell engraftment compared with nontreated mice [23]. In a pilot clinical trial, we demonstrated that HBO therapy given as a single treatment 6 hours before UCB transplantation was well tolerated and resulted in a significant reduction in median EPO level from baseline. Compared with historic controls, HBO-treated patients showed a shorter median time to neutrophil recovery (14 versus 20.5 days). Also, all HBO patients had complete platelet recovery compared with only 69% of controls ($P = .013$), and the HBO-treated patients achieved earlier independence from RBC transfusion [24].

Encouraged by our experience in UCB transplantation, we initiated a pilot study in auto-HCT transplantation. We hypothesized that HBO treatment before HSPC transplantation in auto-HCT will be safe, well tolerated, and associated with lower EPO levels that enhance engraftment in transplanted patients. In this article, we present our findings from a clinical trial investigating HBO incorporation into auto-HCT focusing on HBO safety in this setting and on blood count recovery. We also present data from retrospective analyses evaluating HBO effects on other clinical outcomes, particularly those related to neutropenia.

## METHODS

### *Clinical Study Design*

This was a pilot study primarily investigating the safety of HBO therapy in the setting of auto-HCT. Patients at the University of Kansas Cancer Center were enrolled between March 2014 and December 2014. The study was approved by the institutional review board before initiation of research and was registered at clinicaltrials.gov (NCT02087657). In a study with separate institutional review board approval, we evaluated additional auto-HCT outcomes in our HBO-treated cohort compared with a historic cohort.

### *Patient Eligibility*

We enrolled consenting patients 18 to 70 years of age with NHL, HD, or multiple myeloma who were considered eligible for auto-HCT by the blood and marrow transplant specialists at the University of Kansas Cancer Center. Eligibility for the study was based on a Karnofsky performance status of ≥70% and evidence of adequate hepatic, renal function, pulmonary, and cardiac functions. Minimum standard criteria for transplant included alanine transaminase and aspartate aminotransferase <4 times the upper limit of normal range (as specified by the institution's clinical laboratory), serum total bilirubin ≤2 mg/dL, serum creatinine <2.0 mg/dL, left ventricular ejection fraction ≥45% measured by echocardiogram or multigated acquisition scan, and forced expiratory volume-one second, forced vital capacity, and diffusing capacity of the lungs for carbon monoxide ≥50% of predicted value (corrected to serum hemoglobin). To minimize HBO complications following transplant, patients were excluded from the clinical study if they were pregnant or breastfeeding or had severe chronic obstructive pulmonary disease requiring oxygen supplementation, a history of spontaneous pneumothorax, active ear infection, active sinus infection, history of seizures, claustrophobia, asthma, history of sinus or ear surgery (excluding myringotomy or ear tubes), or uncontrolled viral or bacterial infection at the time of study enrollment.

### *Endpoints*

The primary goal of this study was to evaluate the safety and tolerability of the HBO procedure in these patients. Secondarily, we assessed the impact of HBO on EPO levels following peripheral blood stem cell (PBSC) infusion and its effects on neutrophil and platelet count recovery, in comparison to a historic non-HBO cohort matched for sex, age (within 5 years), disease type (multiple myeloma or lymphoma), and preparative regimen. In a separate secondary analysis, we retrospectively evaluated other outcomes, including transfusion requirements, growth factor use, neutropenic fever, mucositis, and day +100 disease response in our HBO-treated patients who completed therapy (n = 19) and historical controls who received auto-HCT without HBO between January 2008 and December 2012.

### *Treatment*

Patients received standard high-dose melphalan; carmustine, etoposide, cytarabine, and cyclophosphamide; or carmustine, etoposide, cytarabine, and melphalan. After receiving routine day 0 pretransplant clinical and laboratory assessments per institutional guidelines, the patients then presented for HBO treatment. During treatment, patients were exposed to hyperbaric oxygen for 90 minutes after compression to 2.5 atmosphere absolutes in a monoplace hyperbaric chamber (Model 3200/3200R; Sechrist Industries, Anaheim, CA 92807), breathing 100% oxygen. The patients were in the chamber for a total of 120 minutes as approximately 10 to 15 minutes were spent during the compression and decompression phases. Patients also had 10-minute room air breaks every 30 minutes of hyperbaric oxygen treatment. Six hours following the start of HBO therapy, patients received PBSC infusion. Premedications and PBSC infusion followed institutional guidelines. Figure 1A summarizes the study schema.

### *Supportive Care*

G-CSF was started on day +5 post-transplant and stopped after achievement of an absolute neutrophil count (ANC) of ≥1500/$\mu$L or ANC of 500 for 3 consecutive days. Infection prophylaxis consisted of levofloxacin, acyclovir, and oral fluconazole.

### *Assessments*

The safety of HBO therapy was determined based on 2 separate assessments. The first was conducted 24 hours post-HBO therapy and was focused on treatment-limiting toxicities, defined as the occurrence of any of the following complications during or within 24 hours of HBO: seizure disorder, pneumothorax, death or irreversible grade III, or any grade IV toxicity determined by the treating physician to be at least likely related to HBO. The second assessment reviewed any adverse event (AE) that could be attributed to HBO treatment following auto-HCT. Data were collected regarding AEs, severe AEs (SAEs), and their relationship to HBO therapy until engraftment and SAEs until day 100 post-transplant. Toxicities were graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Peripheral blood was also collected from study patients just before starting their preparative regimen, just before HBO therapy on day 0, at 6 hours

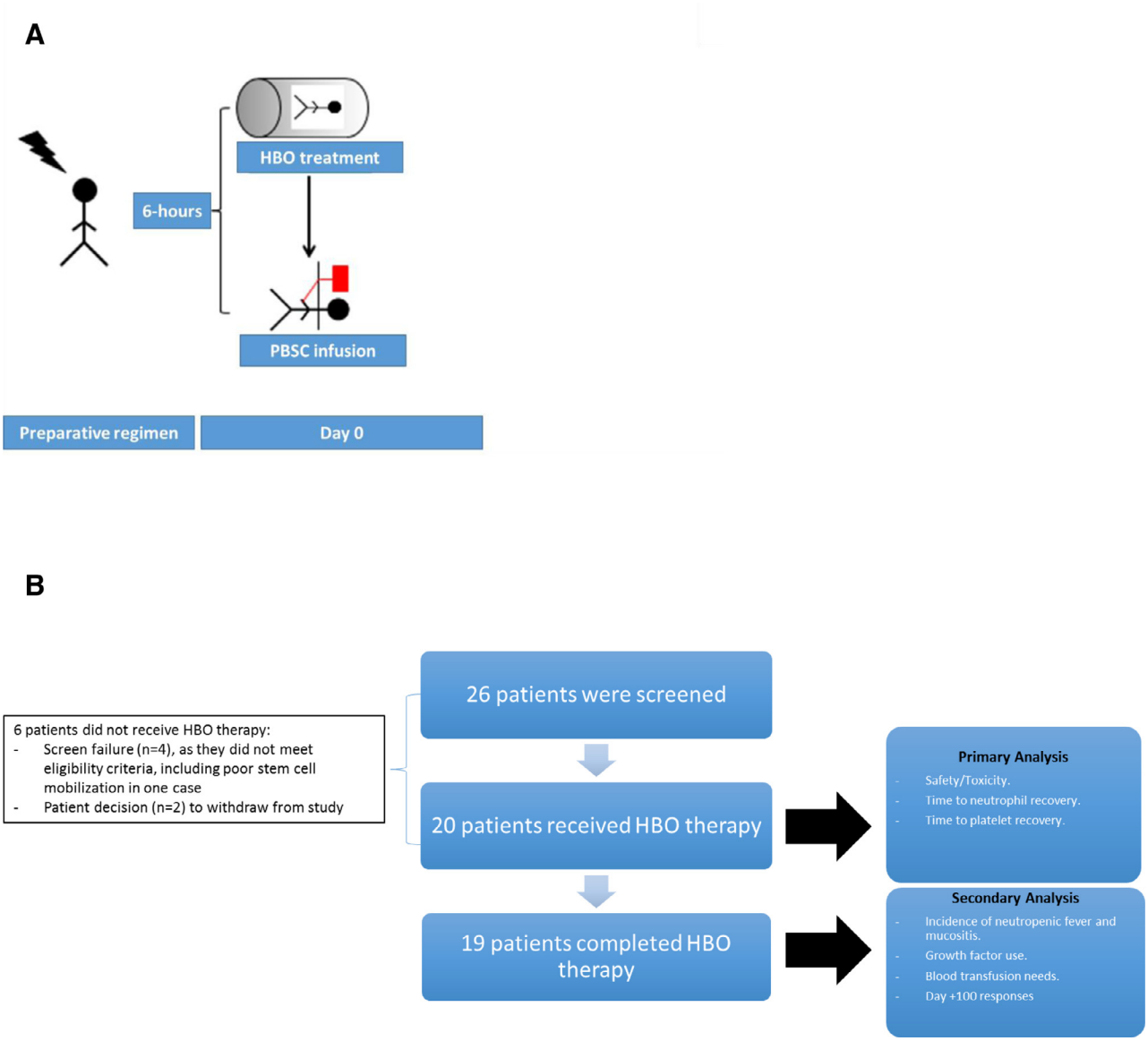


**Figure 1.** (A) Study schema. (B) Patient enrollment.

(just before PBSC infusion), and at 24 and 48 hours from the start of HBO therapy. Blood specimens were processed for plasma isolation and stored by the Biospecimen Repository Core Facility. Samples were evaluated for plasma EPO levels using Human Erythropoietin ELISA Kit (Stem Cell Technologies, Vancouver, British Columbia, Canada) according to the manufacturer's recommendations.

Time to neutrophil and platelet engraftment was also measured. Neutrophil engraftment was defined as the interval between transplantation and the first of 3 consecutive days of ANC $\geq 500/\mu L$; platelet count recovery was defined as the interval between transplantation and the first of 3 consecutive platelet counts $>20{,}000/\mu L$ without a platelet transfusion.

### *Statistical Methods*

Continuous variables were summarized with medians and interquartile ranges (IQRs), and the Wilcoxon rank-sum test was used to compare these variables between the 2 treatment arms. Counts and proportions were used to summarize categorical variables, and Fisher exact test was used to compare these variables between treatment arms. Time to neutrophil recovery and time to platelet recovery were graphically summarized using the Kaplan-Meier method, and arms were compared using the log-rank test. The EPO levels for the pilot cohort were compared between time points using a paired sample *t* test. All *P*values were 2-sided, with $P \leq .05$ being considered statistically significant. Statistical analysis used SAS 9.4 (SAS Institute, Cary, NC).

## RESULTS

### *Patient Characteristics*

A total of 26 patients were screened for this pilot study; 20 were treated and included in the primary analysis (Fig. 1B). These 20 patients had a median age of 63 years (IQR, 14.5 years), 10 (50%) were female, 10 had multiple myeloma, and 10 had HD or NHL. Of the 20 patients treated, 19 completed HBO therapy and were included in the secondary analysis. (One patient completed only 14 minutes of HBO therapy due to ear discomfort and was not included in this analysis; Fig. 1B.) For the retrospective comparison, the control cohort included 225 patients.

Patient characteristics for those who completed therapy (n = 19) are summarized in Table 1. In brief, the median age of patients was 63.3 years in the pilot cohort and 61.5 years in the historic cohort. Males were 47% of the patients (n = 9) in the pilot cohort and 66% of patients (n = 148) in the historic cohorts. Disease status at transplant was reported as first complete remission, second complete remission, first partial remission, stable disease, and progressive disease. The conditioning regimens used were high-dose melphalan; carmustine,

**Table 1**
Patient Characteristics for Secondary Analysis

| Variable | HBO (n = 19) | Historical Control (n = 225) |
|---|---|---|
| Age, median (IQR), yr | 63.3 (16.2) | 61.5 (11.6) |
| Sex, n (%) | | |
| Female | 10 (52.6) | 77 (34.2) |
| Male | 9 (47.4) | 148 (65.8) |
| Diagnosis, n (%) | | |
| HD | 2 (10.5) | 15 (6.7) |
| MM | 9 (47.4) | 148 (65.8) |
| NHL | 8 (42.1) | 62 (27.6) |
| Disease status, n (%) | | |
| CR1 | 6 (31.5) | 63 (28.0) |
| CR2 | 3 (15.8) | 23 (10.2) |
| PR1 | 10 (52.7) | 125 (55.6) |
| PD/SD | 0 | 14 (6.2) |
| Conditioning regimen, n (%) | | |
| Melphalan | 9 (47.4) | 148 (65.8) |
| BEAM | 7 (38.8) | 51 (22.7) |
| BEAC | 3 (13.8) | 26 (11.6) |

MM indicates multiple myeloma; CR1, complete remission; CR2, second complete remission; PR1, first partial remission; PD, progressive disease; SD, stable disease; BEAM, carmustine, etoposide, cytarabine, and melphalan; BEAC, carmustine, etoposide, cytarabine, and cyclophosphamide.

etoposide, cytarabine, and cyclophosphamide; and carmustine, etoposide, cytarabine, and melphalan. Details of disease status and numbers of patients who received different regimens are described in Table 1. Median $CD34^+$ cell dose infused was 3.195 (2.5 to 6.1) $\times$ $10^6$ cells/kg in the HBO group (n = 20) compared to 3.51 (2.2 to 7.5) $\times$ $10^6$ cells/kg in the controls (n = 222, 3 patients with no available data) ($P$ = .2015).

### *Primary Analysis*

*Safety*

Nineteen of 20 treated patients completed the planned therapy without any treatment-limiting toxicities. One patient did not complete the planned therapy per the patient's request because of ear discomfort.

*AEs and SAEs*

*Hematologic AEs and SAEs.* All patients in the pilot cohort had CTCAE grade III/IV leukopenia, neutropenia, and thrombocytopenia. Only 9 patients (47.3%) developed CTCAE grade III/IV anemia requiring packed RBC transfusion.

*Efficacy*

*Blood Count Recovery.* Although the median time to neutrophil count recovery was 11 days in both the HBO and control cohorts, the Kaplan-Meier estimates of the full distributions (Figure 2A) indicate that the time to neutrophil recovery was generally about 1 day sooner for HBO versus historical controls (log-rank $P$ = .005; range, 9 to 13 for HBO patients and 7 to 18 for controls). The median time to platelet count recovery was 16 days (range, 14 to 21) for HBO versus 18 days (range, 11 to 86) for controls (log-rank $P < .0001$; Figure 2B).

### *Secondary Analysis*

*Neutropenic Fever and Mucositis*

The rate of neutropenic fever was 47.4% (n = 9/19) in the HBO cohort versus 62.1% (n = 136/225) in controls ($P$ = .23; Table 2). Mucositis incidence was 26.3% (n = 5) in the HBO cohort compared with 64.2% (n = 138) in controls ($P$ = .002; Table 2). There were no cases of grade IV mucositis in either group, but the combined incidence of grade II and III mucositis was 21% (n = 4) in the HBO cohort compared with 43.6% (n = 98) in controls.

*Hospital Stay and Admission*

The rate of hospital admissions was 31.6% (n = 6) in the HBO cohort compared with 21.6% (n = 45) in controls ($P$ = .39; Table 2).

*Blood Transfusion and G-CSF Support*

The median number of days of G-CSF use was significantly less in the HBO cohort: 6 days (IQR, 6 to 7) compared with 8 (IQR, 7 to 9) days in controls ($P < .0001$). The median number of transfused platelet units was 2 in both groups ($P$ = .57). Grade III/IV anemia requiring packed RBC (PRBC) transfusion was similar in both groups: 9 patients (47.3%) in the HBO cohort versus 109 patients (48.4%) in the historic cohort ($P$ = .55). The median number of transfused PRBC units was 1 in the HBO group and 0 in the historic cohorts ($P$ = .88; Table 2).

*Day +100 Disease Staging Results*

All patients from HBO cohorts were alive at day 100, while 3 from the historic cohort did not survive. Complete remission rate was 57.9% and 52.8% in the HBO and the control cohorts, respectively. The rate of partial remission was 15.8% in the pilot cohort versus 34.3% in this historic control cohort. Finally, the rate of progressive disease was 10.5% in the HBO group versus 7.4% in the control cohort ($P$ = .12; Table 3).

### *Correlative Studies*

*HBO Effects on EPO Levels during Transplantation*

The median EPO level before starting the conditioning regimen was 10.42 (1.5 to 770.6) mU/mL. Median EPO level peaked at 50.66 (3.1 to 269.1) mU/mL after the conditioning regimen and just before HBO therapy. HBO therapy was associated with significant reduction in median EPO levels 6 hours after HBO therapy: 40.65 mU/mL (3.9 to 278.2) post-HBO versus pre-HBO EPO levels of 50.66 (3.1 to 269.1) mL ($P$ = .00018). The median reduction in EPO level was 8.1 mU/mL (15.9%; Figure 3). EPO levels were not examined in the historic controls.

## DISCUSSION

In this article, we present the final results of the first-in-human study evaluating the use of HBO therapy before auto-HCT. We found that standard HBO treatment before auto-HCT is safe and feasible; almost all patients who underwent transplant completed the planned HBO therapy without AEs. Only 1 of 20 patients did not complete HBO therapy because of ear discomfort. In comparison with data from our matched historic cohort, our findings suggest that HBO therapy shortens time to neutrophil and platelet engraftment and reduces the use of G-CSF, with no significant effect on PRBC or platelet transfusion requirements. We understand the limitations of comparing to a current versus historic cohort, but our use of a multivariable model to match groups may have mitigated heterogeneity between the groups. Also, we evaluated the infused $CD34^+$ cell dose in the 2 cohorts as a potential variable that could affect time to neutrophil and platelet count recovery following auto-HCT [26,27]. In our analysis, we did not find significant differences in the infused $CD34^+$ cell dose between the 2 cohorts.

Because EPO negatively affected HSPC homing in our preclinical studies [24], we evaluated HBO effects on serum EPO in our study. We showed that HBO significantly reduced EPO blood levels in the treated patients. However, we have no EPO data from our

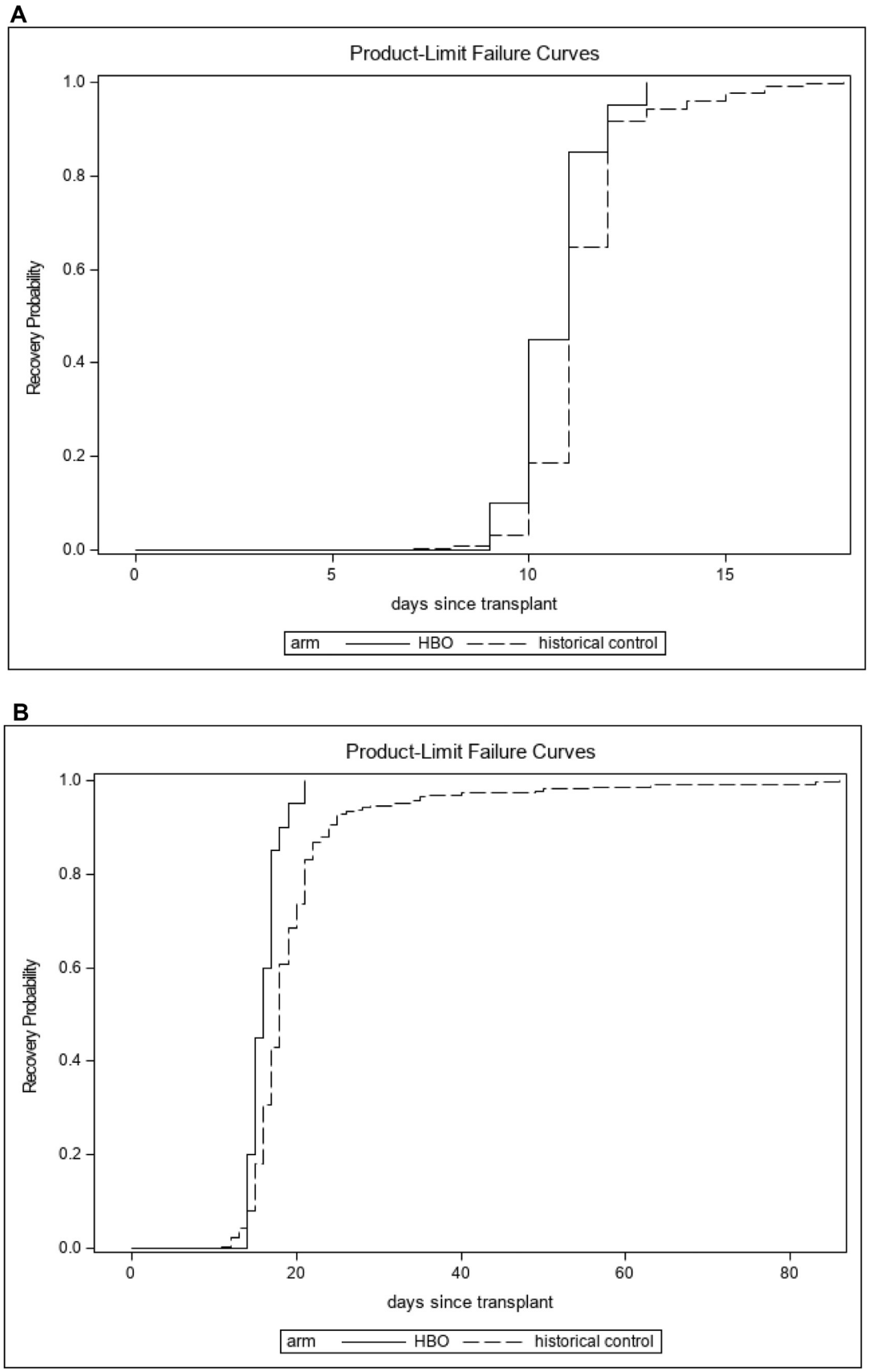


**Figure 2.** (A) Kaplan-Meier curves for time to neutrophil recovery in the hyperbaric oxygen cohort (HBO, solid line) and historical controls (interrupted line). (B) Kaplan-Meier curves for time to platelet recovery in the HBO cohort (solid line) and historical controls (interrupted line).

**Table 2**
Summary of Post-Transplant Outcomes in Secondary Analyses

| Characteristic | Pilot Cohort (n = 19) | Historic Cohort (n = 225) | *P* Value |
|---|---|---|---|
| Neutropenic fever, n (%) | 9 (47.4) | 136 (62.1) | .23 |
| Hospital admissions, n (%) | 6 (31.6) | 45 (21.6) | .39 |
| G-CSF use days, median (IQR) | 6 (1) | 8 (2) | <.01 |
| Mucositis incidence, n (%) | 5 (26.3) | 138 (64.2) | <.01 |
| PRBC units, median (range) | 1 (1) | 0 (2) | .88 |
| Platelet units, median (range) | 2 (2) | 2 (2) | .57 |

**Table 3**
Disease Outcomes at Day 100

| Characteristic | Pilot Cohort (n = 19), n (%) | Historic Cohort (n = 225), n (%) |
|---|---|---|
| Complete remission | 11 (57.9) | 114 (52.8) |
| Partial remission | 3 (15.8) | 74 (34.3) |
| Progressive disease | 2 (10.5) | 16 (7.4) |

Stable disease was reported in 4 patients in the HBO cohort and in 12 patients in the Historic cohort. A total of 9 patients in the Historic cohort were not evaluable (n=3 for death and n=6 had no documented response).

control cohort to optimally study HBO effects on EPO in auto-HCT. Such knowledge might be helpful in deciding which patients might benefit from this intervention. For example, patients with high baseline EPO might benefit more from this intervention.

An interesting finding was that mucositis following auto-HCT is potentially ameliorated by pretreatment with HBO. HBO also appears to reduce G-CSF use, which is a direct result of improvement in time to neutrophil recovery. The use of HBO to improve engraftment in auto-HCT is a novel approach to shorten post-transplant neutropenia, and this approach is both simple and affordable. Other approaches that have been used to improve neutrophil engraftment post-transplant include the use of colony-stimulating factors [28,29]. While G-CSF use improves time to neutrophil recovery, our approach affects other outcomes, including time to neutrophil and platelet engraftment, mucositis incidence, and even the duration of G-CSF use. The mechanism of decreased mucositis after HBO is unclear, but it might be related to direct effects of HBO on oral mucosa. Literature studying HBO effects on radiated mucosa suggests that HBO therapy improves oxygen tension and vascular capacity in irradiated mucosa, but such an effect, which lasted up to 6 months, was documented after 28 successive treatments [30]. In an in vitro study, HBO was found to significantly increase several angiogenic factors, including keratinocyte growth factor in tissue-engineered mucosa following 1 HBO treatment [31]. Accordingly, it is conceivable that 1 single HBO treatment could enhance mucosal healing following chemotherapy by increasing angiogenic factors in oral mucosa.

One concern regarding this intervention is the practicality of this treatment method and applying it to hematopoietic stem cell transplantation. Our completed study [24] and this study consistently show good tolerability and feasibility. Although some centers might not have HBO chambers in their own hospital, most transplant centers will have access to one within a short distance. With the ability to administer the preparative regimen in the outpatient setting, patients can receive HBO as outpatient therapy before their admission to the hospital for their stem cell infusion. The widespread availability of HBO chambers [32] will certainly allow for rapid dissemination of the use of this technology. Also, if future studies show this technology, which is relatively inexpensive, shortens time to blood count recovery, reduces G-CSF use, and reduces post-transplant complications such as mucositis, then the cumulative effect is shortened hospital stay and reduced transplant costs. This potential cost-saving effect might encourage transplant centers to consider housing these chambers in their hospitals or even transplant units. Accordingly, cost analysis of the future randomized clinical trials investigating this technology will help in estimating the cost savings of such treatment.

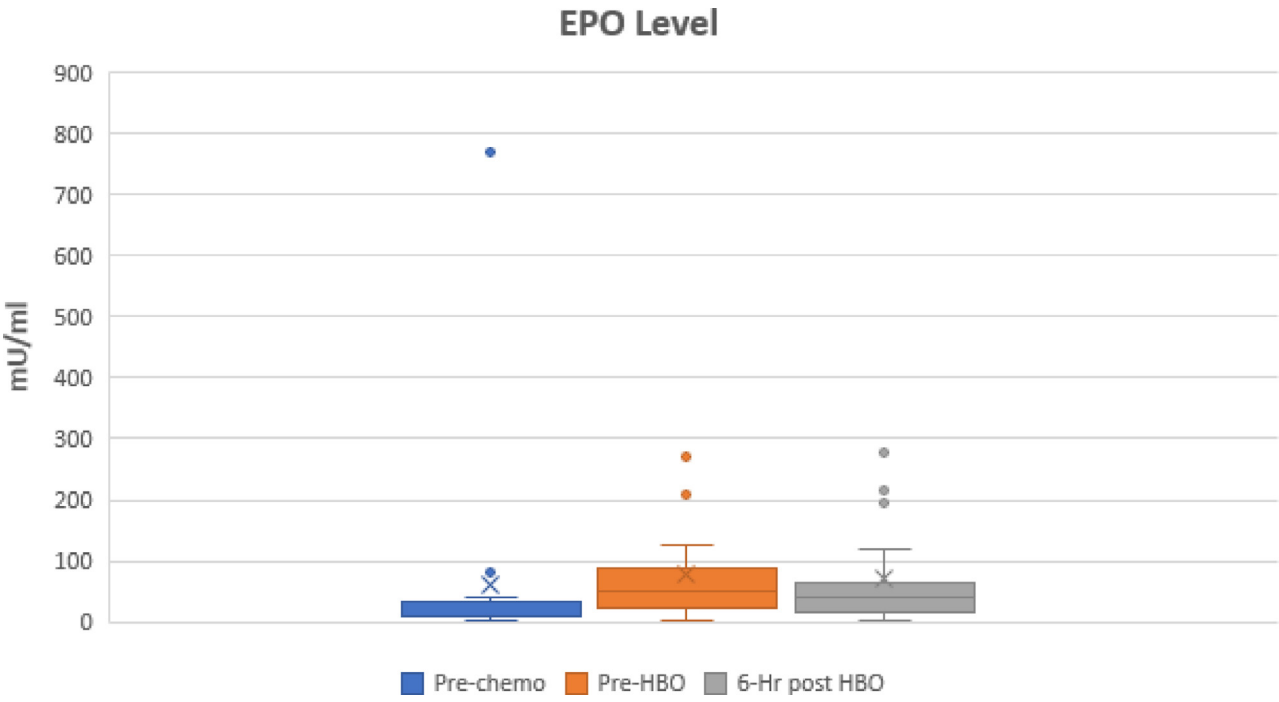


**Figure 3.** Erythropoietin (EPO) response to hyperbaric oxygen (HBO) therapy.

HBO therapy before auto-HCT appears to be well tolerated. Our currently enrolling phase II study (ClinicalTrials.gov identifier: NCT03398200) is focused on HBO's impact on blood count recovery, growth factor use, blood transfusion requirements, and other outcomes following auto-HCT.

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