

## **Hyperbaric Oxygen Decreases Clinical Features associated with Engraftment Syndrome in Multiple Myeloma Patients undergoing Autologous Stem Cell Transplantation.**

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### **Introduction:**

Engraftment syndrome (ES) is a complication of hematopoietic stem cell transplantation (HSCT) commonly presenting as fever, skin rash, and diarrhea and is associated with the elevation of pro-inflammatory cytokines, including interleukin-6 (IL-6) (Spitzer 2001, Maiolino, Biasoli et al. 2003, Khandelwal, Mellor-Heineke et al. 2016). ES can cause significant peri-transplant morbidity, increase the length of hospital stay, and decrease overall survival and non-relapsed mortality (Chang, Frame et al. 2014, ElGohary, Toor et al. 2022).

At our institution, we are conducting phase I-II clinical trials investigating the effect of hyperbaric oxygen (HBO) in patients with multiple myeloma undergoing autologous HSCT. These trials are investigating the effect of HBO on engraftment by suppressing the erythropoietin (EPO) axis, a known disrupter of marrow homing (Aljitiawi, Paul et al. 2016). HBO can also decrease the production of pro-inflammatory cytokines (Benson, Minter et al. 2003, Kudchodkar, Jones et al. 2008) and could therefore theoretically reduce the incidence and or severity of ES.

In this retrospective analysis, we investigate the impact of peri-transplant HBO on the frequency and severity of ES, complications associated with ES, and serum concentrations of IL-6. Since ES manifestations include diarrhea, which overlaps with GI mucositis, we evaluated oral and gastrointestinal (GI) mucositis.

### **Methods:**

Data was collected from electronic medical record from day 5 to day 15 of transplant. Patients were placed in three cohorts including those who did not undergo peri-transplant HBO (n-HBO), received a single treatment of HBO on day 0 of transplant (s-HBO) and received multiple HBO treatments on day 0, +1, and +2 (m-HBO). Patients in the n-HBO and s-HBO cohorts were enrolled in the completed phase II clinical trial (NCT03398200). Patients in the m-HBO cohort were enrolled in the ongoing phase I study (NCT04862676). Grading of oral and GI mucositis was based on the common terminology criteria for adverse events. Enzyme-linked immunosorbent assay (ELISA) for IL-6 was performed from patient plasma samples collected on day +1, +3, +7, and +15 of transplant.

### **Results:**

A total of 87 patients were included in the study. 38 patients were included in the n-HBO and s-HBO cohorts, and 11 were included in the m-HBO cohort. The incidence of ES syndrome, meeting either the Spitzer or Maiolino Criteria, for the n-HBO, s-HBO, and m-HBO cohorts was 27% (95% confidence interval (CI) = 13.8%-44.1%), 21.1% (95% CI = 9.6%-37.3%), and 18.2% (95% CI = 2.3%-51.8%), respectively (Fisher's exact test  $p=0.77$ ). The median number of fever days (defined as a 24-hour period with at least one body temperature reading  $\geq 38^{\circ}\text{C}$ ) for n-HBO, s-HBO, and m-HBO was 1 day (Interquartile range (IQR) 0-2), 1 day (IQR 0-2) and 0 days (IQR 0-1), respectively (Kruskal-Wallis  $p$ -value=0.04) (Figure 1). Any grade oral mucositis incidence was 42.4%, 28.6%, and 0% for n-HBO, s-HBO, and m-HBO respectively (Fisher's exact  $p$ -value= 0.02). There was only one incidence of grade 3  $\geq$  oral

mucositis across cohorts. The median duration of any grade oral mucositis in days was 0 for all cohorts, IQR was 0-3, 0-4, and 0-0, for n-HBO, s-HBO, and m-HBO, respectively (Kruskal-Wallis  $p=0.04$ ). The incidence of any grade GI mucositis was 87.5%, 80%, and 100% for n-HBO, s-HBO, and m-HBO, respectively. There was insufficient evidence of a difference in the incidence or duration of GI mucositis between cohorts. Median peak plasma IL-6 concentration was 11.21 (IQR 5.87-27.92), 14.59 (IQR 5.20-27.80), and 3.44 pg/ml (IQR 1.16-16.29) for n-HBO, s-HBO, and m-HBO, respectively (Kruskal-Wallis  $p=0.1$ ). Pairwise comparisons using mixed models of IL-6 concentration on day +7 of transplant for m-HBO vs. s-HBO, m-HBO vs. n-HBO, and s-HBO vs. n-HBO resulted in  $p$ -values 0.13, 0.11, and 0.85, respectively (figure 2).

#### Conclusion:

In this retrospective study of clinical trial patients, we have shown a significant decrease in clinical features commonly associated with ES, including fever and oral mucositis, in patients receiving m-HBO therapy. These findings may be mediated by a negative regulatory effect of m-HBO on serum concentrations of IL-6. Even though the incidence of ES and peak IL-6 was not statistically different with HBO treatment, we observed less incidence of ES and lower IL-6 concentrations with increasing treatments of HBO. This trend may become significant with a larger sample size.