HBO in Hematopoietic Stem Cell Transplantation: Lessons Learned

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"The problem we are trying to fix"

Clinical HSC transplantation

HSC infusion

Conditioning → Neutropenia → Engraftment

Biologically

HSC BM homing

Prolonged/ delayed in UCB
Impaired in UCB

(Abbreviation: UCB: Umbilical cord blood transplantation; HSC: Hematopoietic stem cells; BM: Bone marrow.)
Hematopoietic stem cell (HSC) homing to bone marrow

Homing is transient; hours to less than 72 hours

SDF-1

CD-34/CXCR4 + Stem cell
HSC homing and erythropoietin (EPO)

Hypothesis: EPO might play a role in HSC homing

Question: How do we lower blood EPO level?

The answer: HBO
Hyperbaric oxygen (HBO)

• Involves inhalation of 100% oxygen intermittently under a pressure greater than 1 atmospheric pressure (ATM)

• Results in:
  a. Mechanical effects related to increased pressure.
  b. Physiologic effects related to hyperoxia.

HBO lowers EPO in healthy volunteers

HBO effects on EPO and UCB CD34+ cell homing/engraftment in a transplant murine model

HBO reduces blood EPO levels at time of HSC infusion → HBO improves early bone marrow homing of HSC → HBO improves HSC bone marrow engraftment

**Aljitawi et al, Unpublished data**

**Aljitawi et al, BCMD (2013)**
From bench to bedside
Hyperbaric oxygen (2.5 atmosphere absolutes and 100% oxygen for 2 hours) is given 6 hours prior to stem cell infusion.
Correlative studies: EPO

**Myeloablative**

**Reduced intensity**

*Lowest EPO level 8-hours from the start of HBO
*EPO rebound noticed 24 hours later

*Aljitawi et al, ASH 2014*
## Blood Count Recovery and Engraftment

<table>
<thead>
<tr>
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<th>HBO (n=8)</th>
<th>Historic (n=31)</th>
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<tbody>
<tr>
<td><strong>Median time to neutrophil recovery</strong></td>
<td>15 (6-25)</td>
<td>18 (5-41)</td>
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<tr>
<td>(Days)</td>
<td></td>
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<tr>
<td><strong>Median time to platelet recovery</strong></td>
<td>33 (30-84)</td>
<td>38(0-161)</td>
</tr>
<tr>
<td>(Days)</td>
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*Aljitiawi et al, ASH 2014*
Would this concept apply to other types of hematopoietic stem cell transplantation?

Autologous peripheral blood stem cell transplantation
Goals

- To determine the safety of HBO in autologous stem cell transplantation.
- To determine HBO efficacy in reducing time to neutrophil and platelet recovery.
Tolerability

• 20 patients treated to date.
• Only one patient was unable to complete the planned therapy.
• No treatment limiting toxicity was observed.
Comparison to historic data:

Neutrophil Recovery

N=12

*Neutrophil recovery was shorter in HBO by an average of 0.3 days.

Aljitawi et al, ASBMT 2015
Comparison to historic data:

Platelet Recovery

N=12

*Platelet recovery shorter in the HBO by an average of 3 days.

Aljitawi et al, ASBMT 2015
Summary

• HBO in HSC transplantation:
  1. Well-tolerated.
  2. Might improve time to neutrophil and platelet count recovery.

• Phase II studies are planned to further investigate HBO effects on HSC engraftment.
Lessons learned

• EPO reduction is followed by EPO rebound.
• Future laboratory studies will focus on:
  a. Timing of HBO
  b. Frequency of HBO
  Can we lower EPO throughout the period of HSC homing?
  Would this lead to further improvement in engraftment?
Concluding Remarks

• New concept: EPO targeting in HSC transplantation.
• Novel approach to improving HSC engraftment: HBO modulates the host microenvironment
• Stay tuned!

We just scratched the tip of the iceberg!
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