Hyperbaric Oxygen for Delayed Radiation Injury

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Disclosures

- None
Cancer Statistics (WHO)

- > 10 million people are diagnosed with CA/year
- 6 million deaths every year
- 12% of deaths worldwide
- 1.2 million new cases diagnosed per year in the USA.
• Half of these patients will become long-term survivors

• Half of these patients will receive radiation treatment
  • Radiation complications in 5-15%

Estimated New Cancer Cases* in the US in 2013

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>28%</td>
<td>29%</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>14%</td>
<td>14%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Melanoma of skin</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>All Other Sites</td>
<td>20%</td>
<td>19%</td>
</tr>
</tbody>
</table>

*Excludes basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.

American Cancer Society
Risk Factors for Radiation Injury

• Treatment Related Factors
  – Size of radiation field
  – Total dose of radiation
  – Radiation per treatment
  – Radiosensitizers/Chemotherapy

Risk Factors for Radiation Injury

• Patient Related Factors
  – Connective Tissue Disease
  – Impaired Genomic DNA repair
    • Ataxia Telangiectasia (1 to 2 % of North American caucasians are heterozygous for ATM)
    • Cockayne Syndrome
    • Nijmegen Breackage Syndrome
    • Xeroderma Pigmentosa
    • Fancony Anemia

Mechanism of Injury

- Hypovascular, Hypoxic, Hypocellular TISSUE
- Replacement of normal tissue with dense fibrous tissue
  - Fibro-atrophic effect
- Progressive Obliterative Endarteritis
- Mitotic cell death with free radical formation and disruption of DNA with inhibition of migration of tissue progenitor cells

Tissue breakdown (Spontaneous or following trauma)
Non-healing lesions
Grafts/Flaps frequently unsuccessful
## Radiation Tissue Injuries

<table>
<thead>
<tr>
<th></th>
<th>Acute</th>
<th>Sub-acute</th>
<th>Delayed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset</strong></td>
<td>During radiation Tx.</td>
<td>2-3 months after radiation</td>
<td>After a 6 month latency or years after exposure or following acute/sub-acute injuries</td>
</tr>
</tbody>
</table>
| **Symptoms** | May be severe, self limited for the most part.  
• Erythema  
• Blistering  
• Sunburned appearance of radiated tissue | Persist for several month, can become chronic  
• Lung (pneumonitis)  
• Spine (demielination) | • ORN (mandible)  
• Enteritis  
• Proctitis  
• Cystitis  
• Necrosis of larynx  
• Chest wall/breast/skin  
• CNS/Spinal cord injury |
Osteoradionecrosis (ORN)

• Incidence: 1-38% following RT
• Presentation:
  – Usually affects the angle of the mandible
  – Persistent mucosal breakdown with bone exposure, fistula or fracture (progressive over time)
  – May be precipitated by trauma or surgery
Osteoradionecrosis (ORN)

Chrcanovic BR et al, Oram Maxillofacial Surg 2010;14:3-16
Radiation Proctitis/Enteritis

- Follows pelvic radiation
- Incidence for chronic 2-20% (may be underestimated)
- Symptoms:
  - Diarrhea, tenesmus, mucus/blood per rectum, pain, fecal urgency, incontinence, strictures-obstruction, fistula formation
Conventional Treatment for Radiation Enteritis/Proctitis

• Medical
  – Steroid enemas, Vit A, Trental

• Endoscopic
  – Argon plasma coagulation, laser, cryotherapy, electrocoagulation

• Surgical
  – Temporary/permanent diverting colostomy (with partial colectomy)
Radiation Cystitis

• Associated with pelvic radiation
  – Approx 20% of px receiving pelvic radiation will have bladder complications
    • Hemorrhagic cystitis accounts for ½ of these complications

• Symptoms:
  – Disurea, polyurea, urgency, incontinence, hematuria
Radiation Cystitis

**Conventional treatment**

**Intravesical**
- Irrigation, alum silver nitrate, PG, formalin

**Systemic**
- Aminocaproic acid, estrogen, sodium pentosanpolysulfate

**Surgical**
- Embolization of hypogastric arteries, urinary diversion, cystectomy
Radiation Damage to Soft Tissues
Chest Wall and Breast

• Incidence is similar to GI/GU
• Symptoms (spontaneous/following surgery)
  – Edema, fibrosis, pain, telangiectasis, skin necrosis, ulceration
Radiation to Larynx

**TABLE 2. GRADING SYSTEM FOR RADIATION REACTIONS OCCURRING IN THE LARYNX AND LARYNGOPHARYNX**

<table>
<thead>
<tr>
<th>Grade*</th>
<th>Symptoms</th>
<th>Sign</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>I</td>
<td>Slight hoarseness; slight dryness</td>
<td>Slight edema; telangiectasis</td>
<td>None</td>
</tr>
<tr>
<td>II</td>
<td>Moderate hoarseness; moderate dryness</td>
<td>Slight impairment of cord mobility, moderate edema and erythema</td>
<td>None</td>
</tr>
<tr>
<td>III</td>
<td>Severe hoarseness with dyspnea; moderate odynophagia and dysphagia</td>
<td>Severe impairment or fixation of at least one vocal cord, marked edema, skin changes</td>
<td>Steam; antibiotics</td>
</tr>
<tr>
<td>IV</td>
<td>Respiratory distress; severe pain; severe odynophagia; weight loss; dehydration; fever</td>
<td>Fistula, fetor oris, fixation of skin to the larynx, laryngeal obstruction, edema occludes the airway, toxicity</td>
<td>Tracheotomy and/or laryngectomy</td>
</tr>
</tbody>
</table>

*Grades I and II are expected side effects of radiation therapy delivered in therapeutic amounts to this region whether or not it is the site of the lesion receiving treatment. Grades III and IV are complications.
HBOT Mechanism of Action

Adequate oxygen tension

Formation of collagen matrix

Neovascularization by stimulation of VEGF

Clinical applications

• Radiation Necrosis of bone and soft tissue

• Wound healing in areas of impaired circulation
HBOT Mechanism of Action

• Oxygen gradient is a powerful stimulus for angiogenesis (durable effect 5y).

• Hyperbaric O2 will enhance:
  – PMN activity.
  – Fibroblast replication.
  – Osteoblast/Osteoclast activity.

• Potent inflammation mediator by blocking ICAM molecules.
UHMS Recommendations for HBO2 in Delayed Radiation Injury

• Osteoradionecrosis and pre-ORN.
• Soft tissue radionecrosis
  – Enteritis/Colitis/proctitis
  – Cystitis
  – Laryngeal necrosis
  – Chest wall/soft tissue non-healing wounds
• Surgical wounding in radiation-damaged tissues

» Hyperbaric Oxygen Therapy Committee 2008 Report
HBO2 & Radiation Damage
Literature Reports of Efficacy

- Cystitis
- Proctitis and enteritis
- Mandible
- Laryngeal/head necrosis
- Chest wall
- Other abdominal and pelvic injuries
- CNS (brain)
- Spine, peripheral nerves, lymphatics
HBO2 in ORN

- Tx with HBO2 is adjunctive to surgical management. Non-viable bone **must** be resected
- HBO2 should precede and follow surgical wounding
- Effect of HBO2 is long-lasting but post wounding course is recommended
### HBO2 in ORN

#### Table 1. Tooth removals in bone-irradiated to dose = 6,800 rads.

<table>
<thead>
<tr>
<th>Group</th>
<th>No. patients</th>
<th>No. teeth</th>
<th>No. osteoradionecrotized sockets</th>
<th>No. patients osteoradionecrotized</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCN group</td>
<td>37</td>
<td>135</td>
<td>31 (22.9%)</td>
<td>11 (29.9%)</td>
</tr>
<tr>
<td>HBO+ group</td>
<td>37</td>
<td>156</td>
<td>4 (2.6%)</td>
<td>2 (5.4%)</td>
</tr>
</tbody>
</table>

*PCN—penicillin.
+HBO—hyperbaric oxygen.

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#### Table 1. Refractory Osteoradionecrosis

<table>
<thead>
<tr>
<th>Previous Treatment Modality</th>
<th>Total No. of Patients</th>
<th>No. with Orecutaneous Fistulas</th>
<th>No. with Pathologic Fracture</th>
<th>No. with Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonsurgical</td>
<td>23</td>
<td>4</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Surgical without hyperbaric oxygen</td>
<td>8</td>
<td>1</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Surgical with hyperbaric oxygen</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Hyperbaric oxygen alone</td>
<td>22</td>
<td>6</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>58</strong></td>
<td><strong>11</strong></td>
<td><strong>11</strong></td>
<td><strong>33</strong></td>
</tr>
</tbody>
</table>
HBO2 in Radiation Hemorrhagic Cystitis

- Corman et al; 57 patients
  - 87% complete resolution/marked improvement
- Nakada et al; 38 patients
  - 90-95% complete/partial resolution
- Chong et al; 60 patients
  - 80% complete/partial resolution
  - 96% complete/partial resolution when treated within 6 months of initiation of sx
- VMMC experience; 60 patients
  - Resolved 37%, improved:49%, on cysto 77% improved
HBO2 in Radiation Enteritis and Proctitis (Hortis IV)

• 150 px randomized to 2.0 vs 1.0 ATA HBO2
  – 30 treatments
  – Blind investigator assessed sx @ 3, 6, 12 months, with follow up to 5 years
  – Crossover at completion of first arm

Results:
1. Decreased LENT-SOMA scores on treatment arm 2.9 (p:0.0019)
2. All treatment effects lost after crossover
3. Significant QOL /bowel sx improvement

HBO2 for Rad. Damage to Soft Tissues

• Pre-op to prevent post surgical complications
  – Univ of Miami, pre head/neck flap, assessing for post op dehiscence
    • 11% vs 48% dehiscence
    • 6 % vs 24 % infection
  – VMMC pre breast reconstruction
    • Case series, unilat breast radiation, anticipating B/L reduction mamaplasty
    • HBOT for all px
    • Results equivalent for both breast

HBO2 for Rad. Damage to Soft Tissues

• Following established injury to heal wounds
  – 23 px with delayed – onset chest wall radionecrosis
  • 8 soft tissue only: 6 of 8 (75%) healed, 4 needed grafts/flaps
  • 15 bony and soft tissue necrosis: 8 of 15 (53%) healed, (all required aggressive debridement and 4 flaps)

Feldmeier JJ. UHMS 1995; 22:383
HBO2 Does Not Stimulate Tumor Growth

• No evidence from clinical reports or registries

• Animal models of transplanted tumors (Squamous cell, prostate cell lines)
  – No acceleration of tumor growth

Chong KT et al. BJUrol Int 2004; 94, 1275-9
Feldmeier JJ. UHMS 2004; 31 (1): 133-45
Contraindications to Elective Hyperbaric Oxygen

- Untreated pneumothorax or history of spontaneous pneumothorax.
- COPD with severe air trapping.
- LVEF≤35%.
- Severe confinement anxiety.
- Inability to communicate or follow instructions.
- Pregnancy.
Complications of HBOT

• Confinement anxiety
• Barotrauma (ears, sinuses, teeth, lungs)
• Reversible myopia - > 20 HBOT sessions
• Hypoglycemia in diabetic patients
• Seizures: 1 in 5,000
• Pulmonary (rare)
  – AGE, Pneumothorax, Pulmonary edema/toxicity
THANK YOU

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