Combination Chemotherapy and Hyperbaric Oxygen: From a Bad Idea to a Good One

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The Mechanism of Chemo

- Chemotherapy works to inhibit DNA replication or function in the cancer cell with the intent of preventing cancer cell replication.
- Unfortunately agents are not selective for cancer cells.
- Rapidly dividing cells (both malignant and benign) are more drastically affected.
- Normal tissues appear to have more successful reparative mechanisms and a deeper pool of stem cells to replace those destroyed by "friendly fire".

Multiple Potential Etiologies Exist For Wound Healing Problems in the Cancer patient Receiving Chemotherapy

- Nutritional Issues
- Immunologic Issues
- The Anti-proliferative Effects of Anti-cancer Therapies
  - Chemotherapy
  - Radiation Therapy

Chemotherapy

- Systemic in Beneficial and Side Effects
- Immunosuppression
  - Decreased Counts
  - Treatable with Antibiotics and Growth Factors
  - Likely to impact the Inflammatory Phase of wound healing
- Nutritional
  - Double Problem of Tumor Parasitic and appetite suppressive effect
  - Enteral and Parenteral Supplements
  - Megace and Marinol

Anti-proliferative Effect of Chemotherapy

- This has always been a concern
- Surprisingly little supporting literature
- Chemotherapy often begun within days of surgery

Chemotherapy

- Systemic in cancer and normal tissue effect
- Types
  1. Alkylators-Cytoxan, Melphalan said to be radiomimetic
  2. Antimetabolites-Methotrexate
  3. Antibiotics-Adriamycin (derived from Streptomyces)
  4. Vinca Alkaloids-Vincristine (from periwinkle plant)
  5. Taxanes-Taxol (Pacific yew tree)
  6. Topoisomerase Inhibitors-Etoposide
  7. Targeted Therapies-Avastin and Erbitux (Monoclonal antibodies) "targeted therapies"
New Agents-Targeted Therapies

- Two New Agents with special issues related to wound healing
  - 1. Erbitux (Cetuximab)-monoclonal antibody that binds to and deactivates EGFR
  - 2. Avastin (Bevacizumab)-monoclonal antibody directed against VEGF

Clinical Chemo Studies

One of the most amazing studies: Colleoni 2006 49 pts with locally advanced breast CA pre-operative-pts went to surgery and additional chemo given in THE RECOVERY ROOM-no detrimental impact on wound healing

Chemotherapy Effects

- Unlike radiation in the scope of effect
- Effects include
  - Immune status-esp during inflammatory phase of wound healing
  - Nutritional status-FOB (fear of barfing)
  - Inhibitory effects on proliferating cells

Special Issues Targeted Therapies

- Avastin-A Special Concern
  Recall Avastin is a monoclonal antibody directed against VEGF
  Several Publications of Wound Healing Issues with and without other agents
  Scappatici 2005 reported enhanced wound complications for pts receiving surgery during chemo vs those operated more than 4 weeks before initiation of chemo including Avastin

Conclusions Based on Pre-clinical Chemo studies

- Chemotherapy can inhibit wound healing
- Impact is transient
- Impact is most pronounced if given during the first several days post wounding, i.e. during the Inflammatory Phase of Wound Healing

In Churchill-Davidson’s Classic Work

- One half of each patients tumor was treated in oxygen at pressure and one half in air with the same dose (1000-1500r)
- Tumors were then biopsied or removed.
- In 6 of 8 cases the response was deemed to be more pronounced in the HBO part
- The study showed the practicality of the approach and served as the model for the next 20 yrs.
Biology of the Oxygen Effect

- The presence of molecular oxygen is likely to increase the production of oxygen radicals.
- More importantly, oxygen combines with the free radical and the molecule with which it has interacted to form a more stable chemical moiety (an organic peroxide).
- In this way, oxygen “fixes” or sets the damage and prevents repair.

Issue of Time element in Maintaining Elevated Levels of O2

- Beppu’s group investigated O2 levels with implanted Clark electrodes in brain tumor patients subjected to 100% O2, osmotic diuretics (mannitol) and HBO both asleep and awake.
- Diuretics and HBO led to increased measured O2 levels.
- In HBO exposure, increased levels were maintained for at least 15 mins.

German Experience in Head and Neck Cancer

- Becker et al 2002 in 7 patients with Eppendorf electrodes measured O2 levels in H&N Ca’s.
- Patients given HBO at 2.4 ATA.
- O2 levels increased from median of 8.6 mmHg to 550 mmHg during HBO.
- Elevated O2 maintained up to 25 mins.

Management of Avastin Wound Complications

- In the Bose article when intestinal perforations result with Avastin therapy, the authors suggest that terminal patients with less than 30 days anticipated survival should be managed conservatively—antibiotics and drains.
- Otherwise surgical intervention should be the same as in a non-Avastin patient.

Special issue—Erbitux

- I could only find one reference in abstract form that suggested a deleterious effect on wound healing.
- Reported an increase in hospital stay and time to drain removal in patients who had received Erbitux pre-neck dissection.
- However, no major wound complications with or without Erbitux.

Review Article: Bose et al Lancet Oncol 2010;11:372-82

- Based on their own experience and compilation of publications recommend:
  1. If chemo is given before surgery, wait a minimum of 6 weeks after Avastin.
  2. If surgery comes before chemo, wait at least 6 weeks to initiate Avastin therapy.
  3. Additional care should be taken depending on the extent of surgery and special caution if bowel is resected.
### Mechanisms Whereby HBO Might enhance Chemotherapy Effects

- 1. Vasoconstriction with reduced edema and enhanced perfusion and delivery of drug
- 2. Enhanced angiogenesis with more vasculature available to carry drug to the tumor
- 3. Enhancement of cell kill by ROS especially for radiomimetic drugs such as alkylators

### Problems with these Papers

- Mixed Grade 3 and Grade 4 tumors
- Chemotherapy was a mixed bag
- Since Radiation was included cannot say whether sensitization was to chemo or rads or both
- For CNS tumors chemo has problems with penetration beyond the blood brain barrier
- Improvements were only modest

### Series of Japanese Papers with Malignant Gliomas

   HBO+XRT+nirosourea Chemo-improved survival; no unexpected toxicity 15 pts
2. Ogawa K Radiotherapy and Oncology 2003
   HBO+XRT+procarbazine, nimustine and vincristine 21 pts modest improvement in time to progression
   Improved survival compared to historic publications
4. Ogawa K 2011 Int J Radiat Oncol update 59 pts. no unexpected toxicity better median survival compared to other published results

### Additional Experience

- Beppu et al 2003 Morioka Japan
- 39 patients (29 GBM, 10 AA) radiation, HBO and ACNU and interferon-beta
- 39 patients enrolled; 35 completed full therapy
- Response rates GBM, AA, overall: 50, 30 and 43%
- Time to tumor progression: 38, 56 and 43 weeks

### Radiation after HBO (contd)

- In 2nd report, 15 patients treated at 2 centers: One center XRT within 15 mins (11)-other center XRT within 30 mins (4)
- Results were compared to 14 others without HBO
- (Kohshi et al 1998)

### Beppu’s Experience

- Radiation within 15 minutes of HBO (2.8 ATA)
- Chemotherapy at least 2 hrs after HBO
- No unexpected toxicity except one with severe otic barotrauma
Other Human Experience

- Heys SD 2006 University of Aberdeen UHM 2006
- 32 pts with locally advanced breast CA
- Randomized 15 received 10 pre-chemo HBO treatments prior to chemo consisting of Adriamycin, Cytoxan and Vincristine
- No difference in tumor response or survival
- Intent to see if HBO could improve vascularity and thus drug delivery

Pre-clinical Papers 1

- Alagoz 1995 Cancer evaluation of HBO2 as Chemosensitizer for Ovarian Ca in a model of transplanted tumor in mice
- In HBO group “5 priming dives” to enhance angiogenesis and drug delivery
- Animals received Cisplatin IP
- In HBO group tumor vascularity and tumor response significantly increased

Ohguri T- Int J Hyperthermia

- 22 patients 16 received HBO
- All received chest hyperthermia and chemo with Taxol and carboplatnin for lung metastases secondary to non-small cell lung cancer
- Median time to progression 9 months with HBO and 8 without HBO

Pre-clinical 2

- Takiguchi N Cancer Chemother Pharmacol 2001
- Transplanted sarcoma in mice treated with SFU
- 4 grps: 1) control 2) HBO only 3) chemo only 4) chemo + HBO
- Growth was suppressed most in combined group
- HBO and Chemo alone suppressed growth compared to control
- Measured values of drug in tumor, liver and kidney but not brain were increased

Preclinical 3

- Petre P J Thoracic Surgery 2003
- Transplanted sarcoma in rats as model of lung metastases
- Study included cell culture
- Cells and animals received Adriamycin
- Both cell kill in culture and number of metastases improved with addition of HBO to adriamycin

Results of Phase I Study
Sponsored by the Baromedical Research group

- Abstract published in the Proceedings of the ASCO Meeting 2010
- 10 of 12 pts completed study
- 2 left the study: 1 non-compliance and 1 for distant metastases (liver and bone)
- No dose limiting toxicity from HBO
- 25% required myringotomies
- Average time between HBO and rads 10.2 minutes
- Initial complete tumor response seen in all 10 pts.
- Plan is to complete a Phase III trial
Pre-clinical 4

- Stuhr L: Cancer Letters 2004
- Animal model of mammary tumors induced by the application of DMBA
- HBO alone and HBO + 5FU decreased tumor volume
- Tumor vascularity was less in the HBO treated animals

Conclusions

- 1. In both animal and human experience chemotherapy toxicity does not appear to be enhanced by HBO
- 2. In the experience with malignant gliomas it is hard to tease out mechanism of improvement in survival since patients also received radiation
- 3. In the preclinical studies the effect of some drugs that do not work through ROS also seem to be improved suggesting that it is a delivery effect
- 4. The question of enhanced angiogenesis in tumor is not consistently seen and if so may overall be a bad effect due to likelihood of enhanced metastases.

Conclusions 2

- 5. It is certainly easier to deliver chemotherapy during an HBO treatment than it is to deliver radiation
- 6. The results to date merit additional study