Hyperthermia in Oncology: The Hot Topic

Gurdev Parmar, ND, FABNO

Fort Langley, B.C., Canada

info@integratedhealthclinic.com

www.integratedhealthclinic.com/blog
Disclosure Statement

• Owner Integrated Health Clinic, which offers Hyperthermia Treatment

• Co-Investigator of pending Phase II trial “Neoadjuvant local regional hyperthermia for advanced local pancreatic cancer: a randomized clinical trial”
“Those who cannot be cured by medicine can be cured by surgery. Those who cannot be cured by surgery can be cured by fire [hyperthermia]. Those who cannot be cured by fire, they are indeed incurable.”

—Hippocrates (479–377 B.C.)
Hyperthermia through the Ages

• Pitta

• Yang

• Fire

• Heat

• Every traditional medical culture has described hyperthermia, and its uses in healing.

• Ancient texts from India, China, Egypt, Turkey, Middle East and others, contain pictures of various techniques being used to impart heat - in attempts to treat rounded lesions above and below the skin.
Hyperthermia (HT) Basics

- Causes direct cytotoxicity \(^{1-6}\)
- Known chemotherapy (CT)sensitizer \(^{7-16}\)
- Known radiation (RT) sensitizer \(^{17-23}\)
- Improves tumour oxygenation \(^{24-26}\)
- Induces P53 \(^{27,28}\)
- Improves delivery of liposomal drugs \(^{29-31}\)
Challenges in HT

– The 3 major challenges are;

• Heating tumours to high temperatures in a precise and reproducible manner*

• Defining and calculating the required “thermal dose” for efficacy*

• Measuring temperature (dosimetry);
  – Historically invasive
  – Improved recently with 3D MRI–based thermometry
  – Beyond the scope of today’s lecture

– There has been significant progress on all these issues, particularly in the past decade
HT Findings to Date

- Many positive published randomized trials on HT in human cancer patients\textsuperscript{7–23}

- Most trials on HT + RT and/or CT have demonstrated a significant improvement to:
  - Local tumour control
  - Survival advantage

- Will review most recent & best evidence later in this discussion
Hyperthermia became part of the professional handbooks

Cumulative publications

(hyperthermia OR heat-treatment OR heat-therapy) AND (oncolog* OR tumor OR cancer OR neoplasm) NOT (malignant–hyperthermia)
Limits of this lecture

• In this lecture HT will be defined as;

  – 40°C to 45°C Range:
    – Average body temperature is 37°C+/- 1.5°C
    – Range desired in local/regional HT
    – Difficult range to accomplish in whole body hyperthermia (WBH)

  – Known benefits both below & above this range;
    • Below: Circulatory, Detoxifying & Immunogenic effects (WBH)
    • Above: Ablative indications (Local/Surgical HT)
Mild to Moderate HT: Quick Review

• **Mild HT:**
  – 37°C to 38.5°C range
  – Potential benefits include improved circulation and detoxification
  – Most accessible forms of mild HT include:
    • Sauna
    • Hot baths
    • Balneotherapy

• **Moderate Hyperthermia (fever range):**
  – 38.5°C to 40°C range
  – Added immunogenic benefits like those seen in infection
  – Most often used range in WBH
    • Requires specialized equipment & screening ECG/exams
    • Requires monitoring rectal temperature, vitals, I.V. fluids
HT Dosimetry: Arrhenius Relationship

• In HT, this is the math defining “Thermal Dose”, or how much heat is required

• Defined as the log of the slope (1/ Do) of cell survival curves, as a function of temperature$^{33}$ (Fig.1)

• Defines temperature vs. cell killing rate relationship

• Used as measure of thermal dose in human trials$^{32}$

• Arrhenius plots from in vitro and in vivo studies correlate well$^{35}$
Figure 42-1  ■ (A) Cell survival curves for V79 cells, plotted as log of surviving fraction as a function of time of heating at a defined temperature. Source: Data re-plotted from Reference 122. (B) Arrhenius plot from same data. Note change in slope of Arrhenius plot above and below 43°C.

Viglianti BL, Stauffer P, et al. Cancer Medicine 8, Chapter 42, Fig.1, 2010
Dosimetry: BreakPoint

• The “breakpoint” is the temperature where the slope changes significantly\textsuperscript{32-35}

• The breakpoint for human cells is near 42-43°C
  – Above the breakpoint;
    • Increase of 1.0°C doubles the rate of cell killing
  – Below the breakpoint;
    • Decrease of 1.0°C drops rate of cell killing by a factor of 2-4 times

• The change in slope below the breakpoint is largely due to development of thermotolerance during HT
Factors affecting the Arrhenius Relationship

• Three cellular/tissue responses to HT which are known to affect its cytotoxicity include;
  
  – Thermotolerance
  
  – Acute Acidification
  
  – Step-Down Heating

• All 3 factors affect the position and slope of the Arrhenius plot

• Thereby impacting the cytotoxicity of HT significantly (Fig.2)
Thermotolerance

• Refers to the development of resistance to HT from prior exposures to heat

• Repeated heating at temperatures below the breakpoint (<42°C) allows thermotolerance to develop

• Heated cells produce HSP’s, particularly HSP70 and HSP27, in response to environmental stressors such as extreme heat, which protect the heated cells against further heating

• Quercetin and other COX-2 inhibitors have been found to minimize thermotolerance, thereby improving HT sensitivity
Acute Acidification

• Increasing acidity in the target tissue sensitizes cells to killing

• Acute acidification shifts Arrhenius plot to the left (Fig.2), causing breakpoint to nearly disappear

• Acute acidification also inhibits thermotolerance

• Methods for acute acidification of the tumour environment have been studied extensively in pre-clinical models and in humans\textsuperscript{38-40}

• Administering glucose during HT seems to be the most effective means to acutely acidify\textsuperscript{40}
Step-Down Heating

- Involves raising temperatures above the breakpoint, then dropping it below breakpoint for remainder of the treatment\textsuperscript{41}

- Occurs clinically when heat is turned down in response to:
  - Pain
  - Excessively high tissue temperatures
  - Perfusion or edema occurs or increases

- Prevents thermotolerance during HT treatment (which shifts Arrhenius plot to the right)
Oxygenation from HT

- Some of the clinical benefits of HT result from improvements in oxygenation\textsuperscript{42-44}

- Studies in rodent, canine and human tumours have shown improved tumour oxygenation by HT, including breast cancer\textsuperscript{42-44}

- Increased oxygenation begins at lower temperatures (40-43°C)

- Some human trials have shown that failure to re-oxygenate after the first HT fraction, significantly reduced the pathologic complete response rate at the time of surgery, breast cancer in this case (Fig.5)\textsuperscript{42}
Figure 42-5 Relationship between change in Eppendorf electrode hypoxic fraction, as measured 24 hours post first HT, and clinical response in patients with locally advanced breast cancer. These patients were treated with a combination of Taxol, RT, and HT. Re-oxygenation is clearly associated with those patients who achieved either a complete or a partial response. (Ref 42)

Viglianti BL, Stauffer P, et al. Cancer Medicine 8, Chapter 42, Fig.5, 2010
Immune Effects of HT

• Immune enhancing effects of HT include:

  – Enhanced cytotoxic activity of macrophages, T cells & NK Cells\textsuperscript{45-47}

  – Enhances maturation and function of dendritic cells \textsuperscript{48-50}

  – Improved immune cell-mediated recognition and attack of heated tissue \textsuperscript{51-56}
Immune Effects of HT

– Continued Immune Effects....

– HSP’s expressed on the surface of heated tumour cells activate NK cell proliferation and thus tumour cell cytotoxicity 27,28,51,53,54

– HSP/NK cell mechanism makes heated tumour cells more immunogenic 51-54

– Leads to a cytokine release and increased expression of antigen-presenting cell surface molecules, thus a more effective adaptive immunity 55,56
Vascular Response to HT

• Increased blood flow is the first tissue reaction to occur at 41°C to 41.5°C (in the skin)\textsuperscript{57}

• Estimated that muscle/skin perfusion increases approximately 10-fold, whereas tumour perfusion increases by only 1.5 to 2-fold\textsuperscript{58}

• At higher thermal doses (>45°C) there is an increased vascular permeability, which can lead to edema and/or vascular stasis/hemorrhage

• Physiologic changes in tumours at 40-42°C in Fig.3
Physiological Benefits of Low Temperature Hyperthermia (40-42°C)

Apoptosis + Respiration Inhibition

Increased Vessel Pore Size

Reoxygenation

Increased available interstitial volume fraction

Increased Macromolecular and Liposomal Drugs Delivery

Increased Perfusion

Viglianti BL, Stauffer P, et al. Cancer Medicine 8, Chapter 42, Fig.3, 2010
Molecular Effects of HT²

Cell Membrane/Cytoskeleton
- Changes in fluidity and stability of cell membrane
- Changes in Cell Shape
- Impaired Transmembranal Transport
- Changes in Membrane Potential
- Modulation of Transmembranal Efflux Pumps
- Apoptosis Induction

Other Alterations of Cell Function
- Intracellular metabolism of other substrates
- Gene expression, signal transduction
Molecular Effects of HT$^2$

Intracellular Proteins
- Impairment of Protein Synthesis
- Protein Denaturation
- Aggregation of Proteins at the nuclear matrix
- Induction of HSP-synthesis

Nucleic Acids
- Impairment of RNA/DNA Synthesis
- Inhibition of Repair enzymes
- Altered DNA conformation
Chemosensitizing Effects of HT

• HT accelerates the primary mode of action of various CT drugs including\textsuperscript{7-16};
  – Alkylating action
  – Induced protein damage & DNA strand breaks
  – Production of oxygen radicals

• Many CT agents shown to improve with HT, including; melphalan, cyclophosphamide, nitrogen mustards, anthracyclines, nitrosureas, bleomycin and mitomycinC\textsuperscript{59-61}

• Lack of Interaction has been found with etoposide and vinca alkaloids\textsuperscript{59}
## Complimentary Effects of Chemotherapy & Hyperthermia

<table>
<thead>
<tr>
<th>Effects/Method</th>
<th>Chemotherapy</th>
<th>Hyperthermia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Place of Primary Activity</td>
<td>Near Arteries</td>
<td>Far from arteries</td>
</tr>
<tr>
<td>Reaction Rate</td>
<td>Normal</td>
<td>Enhanced</td>
</tr>
<tr>
<td>Chemo Penetration</td>
<td>Low, due to high pressure</td>
<td>Enhanced via electro-osmosis</td>
</tr>
<tr>
<td>Chemo Metabolism</td>
<td>Normal</td>
<td>Enhanced</td>
</tr>
<tr>
<td>Chemo Selection</td>
<td>Limited by chemical reaction</td>
<td>Local enhancement</td>
</tr>
<tr>
<td>Cell Division</td>
<td>Acts in M + G2 Phase</td>
<td>Acts in S Phase</td>
</tr>
<tr>
<td>Activity</td>
<td>No Activity in G0 Phase</td>
<td>Decreases time spent in G0 Phase</td>
</tr>
<tr>
<td>Treatment Failure</td>
<td>Blood/Organ failure and tolerance</td>
<td>Resensitizes to chemo &amp; decreases liver and kidney stress</td>
</tr>
</tbody>
</table>
**G_{2}**

The cell “double checks” the duplicated chromosomes for error, making any needed repairs.

**S**

Each of the 46 chromosomes is duplicated by the cell.

**G_{1}**

Cellular contents, excluding the chromosomes, are duplicated.

**Mitosis**

**Cytokinesis**

**G_{0}**

Cell cycle arrest.
Radiosensitizing Effects of HT

• Complementary effects between RT and HT include\textsuperscript{17-23,62,63};

  – Cells in S-phase relatively resistant to RT, but most sensitive to HT

  – Hypoxic cells 3 times more resistant to RT than aerobic cells, whereas no difference in thermal sensitivity between aerobic and hypoxic cells

  – Good evidence in human soft tissue sarcoma and locally advanced breast cancer, that HT causes re-oxygenation, further improving RT response\textsuperscript{18,22}

  – HT inhibits the repair of protein damage, by inactivating crucial DNA repair pathways\textsuperscript{62,63}
# Complimentary Effects of Radiotherapy & Hyperthermia

<table>
<thead>
<tr>
<th>Effect/Method</th>
<th>Ionizing Radiation</th>
<th>Hyperthermia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell Cycle Specificity</td>
<td>Acts in M + G1 Phase</td>
<td>Acts in S Phase</td>
</tr>
<tr>
<td>pH-Dependance</td>
<td>Acts in relatively ALKALINE environments</td>
<td>Acts in relatively ACIDIC environments</td>
</tr>
<tr>
<td>Oxygen Specificity</td>
<td>Acts in Well-Oxygenated environments</td>
<td>Acts in Hypoxic tissue</td>
</tr>
</tbody>
</table>
Phase 3 Trial: HT in Sarcoma

- Recent phase III, randomized, multi-centre (EU & US), clinical trial comparing HT+EIA (etoposide, ifosfamide and adriamycin) vs EIA alone

- 341 patients with locally advanced soft tissue sarcomas with a median follow-up of 34 months

- 2 year disease free survival (DFS) 70% (HT/EIA) vs 57% (EIA)

- 2 year local progression free survival (LPFS) 92% (HT/EIA) vs 80% (EIA)

- Patients more likely to experience local progression or death in EIA-alone group (relative hazard [RH] 0.58, 95% CI 0.41–0.83; p=0.003)
Phase 3 Trial: HT in Sarcoma

- Treatment response rate was 28.8% (EIA/HT) vs 12.7% EIA (p=0.002)

- Overall survival (OS) was better in the EIA/HT group (p=0.038)

- As a result of this study - The National Clinical Practice Guidelines in Oncology for Soft Tissue Sarcoma (NCCN), now recommends HT + CT for Stage II, III and IV soft tissue sarcomas of the trunk and the extremities

- Used to be recommendation in only Stage IV, but the results of this study showed a significant benefit for Stages II, III and IV
Phase 3 Trial: HT in Cervical Carcinoma

• 361 patients with previously untreated locally advanced pelvic tumours randomized to RT vs RT+HT\textsuperscript{17}

• Included patients with rectal, bladder, and cervical carcinoma

• Complete response (CR) rates were 39% after RT alone and 55% after RT+HT (p ≤ 0.001)

• Results best in cervical carcinoma where CR rate following RT + HT was 83% compared with 57% after RT alone

• 3-year survival was 27% RT alone vs. 51% RT+HT (p = 0.003)
A

361 patients randomized

182 assigned radiotherapy plus hyperthermia
179 assigned radiotherapy alone

182 assessable
176 assessable
3 did not start radiotherapy

B

Cervix

RT+HT

RT

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>RT+HT</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>RT</td>
<td>58</td>
<td>43</td>
<td>26</td>
<td>17</td>
<td>17</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>56</td>
<td>36</td>
<td>17</td>
<td>9</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

Viglianti BL, Stauffer P, et al. Cancer Medicine 8, Chapter 42, Fig.8, 2010
Phase 3 Trial: HT in Breast Cancer

• 5 independent phase 3 trials were combined for this international collaborative study\(^1\)

• Patients randomized to RT or RT+HT

• Significant improvement in CR for HT + RT vs. RT alone, 59% and 41% respectively (odds ratio 2.3 (95% CI 1.4-3.8))

• Greatest effect observed in patients with recurrent lesions in previously irradiated areas, since further irradiation was limited to low dosages

• Did not show an overall survival advantage
Phase 3 Trial: HT in Head & Neck Cancer

• This study randomized 65 patients to RT alone versus RT + HT

• HT twice weekly, 72 hours apart

• Stage III: CR 58% RT+HT vs 20% RT alone

• Stage IV: CR 38% RT+HT vs 7% RT alone

• No additional benefit in stage I & II, with >90% achieving a CR in both groups
Phase 3 Trial: HT in Malignant Melanoma

• 70 patients with metastatic or recurrent malignant melanoma lesion(s) were randomized to RT or RT+HT\textsuperscript{21}

• Significant benefit for RT+HT with a 2-year local control of 46% vs. 28% RT alone

• Quality assurance was an issue in this trial since only 14% of treatments achieved 43°C for 60 minutes, the target thermal dose for treatment

• Despite this inconsistency in thermal dose, positive benefits were seen - presumably due to the known benefits at lower doses (40-42°C (Fig. 3))
Phase 3 Trial: HT in Glioblastoma Multiforme

- University of California San Francisco study comparing interstitial HT + Brachytherapy vs. Brachytherapy alone

- 112 patients with glioblastoma multiforme were accrued, 79 qualified for brachytherapy and were randomized

- Remaining patients were dropped from the protocol due to disease progression

- Both time to tumour progression and overall survival were significantly improved vs. brachytherapy alone

- Two-year survivals were 31% and 15%, respectively
HT Availability in USA


- [hyperthermia.mc.duke.edu/](hyperthermia.mc.duke.edu/)

- [bichercancerinstitute.com/](bichercancerinstitute.com/)

- [radonc.ucsf.edu/treatment_programs/hyperthermia.html](radonc.ucsf.edu/treatment_programs/hyperthermia.html)

- [cancercenter.com/conventional-cancer-treatment/radiation-therapy/local-hyperthermia.cfm](cancercenter.com/conventional-cancer-treatment/radiation-therapy/local-hyperthermia.cfm)
REFERENCES

• HT CYTOTOXICITY:
• HT + CT:
REFERENCES


• HT + RT:
REFERENCES


24. OXYGENATION:


27. HEAT SHOCK PROTEINS (HSPs):


29. HT + LIPOSOMAL DRUGS:


REFERENCES


• ARRHENIUS PLOTS & CEM 43°C:

• THERMOTOLERANCE:

• ACUTE ACIDIFICATION:
REFERENCES

• STEP DOWN HEATING:

• HT & OXYGENATION:

• NK CELLS, T CELLS & MACROPHAGES:

• DENDRITIC CELLS:
REFERENCES

• TUMOUR IMMUNOGENECITY:

• VASCULAR RESPONSE:

• CHEMOSENSITIZING:
REFERENCES:


• RADIosenSITIZING:


• TEXTBOOKS USED AS GENERAL REFERENCES:

– Viglianti, BL, et al. (2010), Chapter 42: Section 10 Radiation Oncology, Cancer Medicine 8; Pg. 528-540. Shelton, CT, USA. PMPH-USA Ltd.

Hyperthermia in Oncology: The Hot Topic

Gurdev Parmar, ND, FABNO

Fort Langley, B.C., Canada

drgparmar@integratedhealthclinic.com

www.integratedhealthclinic.com/blog