Hyperthermia

Chapter 28
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Introduction

• Heat was used in many cultures for almost any disease including cancer
  – First case of a patient with a breast tumor treated with hyperthermia was described more than 3,500 years ago
  – In 1866 a case was described where sarcoma disappeared after prolonged infection with a high fever causing bacteria
  – 1898 marked regression of carcinomas of the uterine cervix after local hyperthermia

Recent history

• Studies in the 1970s – 1980s demonstrated highly quantifiable, time dependent cytotoxic effects of heat (41-45°C) on cells
  – Similar to highly reproducible and predictable effects of radiation
• In combination with radiation heat was found to have both additive and synergistic radiosensitizing properties

Hyperthermia definition

• Hyperthermia is defined as a therapeutic procedure used to raise the body or local tissue temperature to about 41-43°C (42.5°C threshold)
• It is almost always used as adjuvant therapy as it provides a possibility for synergy with different actions of conventional therapies
  – Combination with radiotherapy and/or chemotherapy results in higher response rates, improved tumor control, better palliative effects and/or better overall survival rates in some tumor types

Direct effects of hyperthermia

The general shape of cell survival curves is similar to those obtained for x-rays

• Differences compared to radiation:
  – Two parameters: temperature and exposure time
  – Low temperature curves flatten out (thermal tolerance)
  – The amount of energy involved in cell inactivation is ~1000 times higher in hyperthermia

Direct effects of hyperthermia

• The change in slope identifies a “breakpoint” of ~43°C for human cells
• The difference in activation energy corresponds to a difference in cell killing rate
• Different mechanisms or development of thermal tolerance may be involved
### Cytotoxic effect of hyperthermia

- The activation energy for heat cytotoxicity is similar to that for protein denaturation (130-170 kJ/mol).
- The target for heat cell killing in this temperature range resides in cellular proteins.
- Additional evidence is the importance of heat shock proteins (HSPs) in protecting thermotolerant cells from thermal damage.
  - One of the primary functions of HSPs is to stabilize and refold other proteins that have been denatured or damaged.
  - HSPs production is enhanced in response to such events.

### Biological effects of hyperthermia vs. radiation - additive

- Since killing is associated with degradation or denaturation of proteins, hyperthermia induces effects in both the nucleus and cytoplasm.
  - Radiation cell killing primarily damages DNA.
- In organized tissues heat damage occurs more rapidly than radiation damage.
  - Both differentiated and dividing cells are killed by heat.
- The DNA repair process is heat-sensitive, making cells in S-phase a primary target.
  - Cells in M and G2 phases are the most radiosensitive.

### Biological effects of hyperthermia vs. radiation - sensitizing

- At the cellular level: the events associated with heat radiosensitization involve DNA damage and the inhibition of its repair.
  - The role of heat is to block the repair of radiation-induced lesions.
- At the tissue level: even mild hyperthermia promotes changes in tumor environment, providing sensitization via oxygenation, change in pH, metabolism, protein/gene expression, and vascular perfusion.

### Role of tumor micro-environment

- Malignant and normal cells demonstrate no difference in their response to heat under identical culture conditions.
- The combination of low pH, low oxygen tension, and lack of glucose and other nutrients tends to make cells extremely responsive to elevated temperatures.
- The microenvironment of cells in solid tumors is particularly conducive to heat sensitivity.

### Thermal enhancement ratio

- The thermal enhancement ratio (TER) is defined as the ratio of doses of x-rays required to produce a given level of biologic damage with and without the application of heat.
- Characterizes the extent of the interaction of heat and radiation (both additive and sensitizing effects).
- The TER has been measured for various normal tissues (skin, cartilage, and intestinal epithelium).
- The data form a consistent pattern of increasing TER with increasing temperature.

### Thermal enhancement ratio

- TER for tumors (points) and normal tissues (range indicated by two curves).
- TER also depends on temperature, time at that temperature, and time interval between irradiation and heat.
- In clinical evaluations TERs of only 1.15 to 1.5 were observed.
Therapeutic gain factor

- The therapeutic gain factor can be defined as the ratio of the TER in the tumor to the TER in normal tissues.
- For the same environmental conditions normal tissues and tumor have the same sensitivity to heat.
- The therapeutic gain is typically achieved due to higher temperature and more heat-sensitive microenvironment of the tumor.

Thermal tolerance

- Resistance to subsequent heating was found in cell cultures, mediated by heat-shock proteins (HSP).
  - HSP are “chaperon” molecules, assisting with folding and unfolding of macromolecular structures; they are also produced after treatment with other toxic agents, e.g., arsenic and ethanol.
- Possible problem scheduling fractionated heat treatments.
- Recent findings: heat-induced radiosensitization is not subject to thermal tolerance.
- The effect of reduced direct cell killing is overcompensated in situ by radiosensitization.
- Current effort in exploration of HPS role in promoting antitumor immune response.

Immunologic effects of hyperthermia

- When body temperature is elevated through fever, it is usually <40°C.
- Reports of improved survival in patients with highest fevers.
- Enhancement in immune system response (including adaptive response through effector T-lymphocytes) is implicated.

Mechanisms of immune activation:

(A) Heated tumor cells increase the surface expression of signaling molecules, making the tumor cells more sensitive to lysis by NK cells and CD8+ T cells, respectively.
(B) Heated tumor cells release HSPs, which activate NK cells and APCs. HSPs contain potential tumor antigens, and APCs take up the HSP-antigen complex and cross present the antigen to CD8+ T cells.
(C) Heated tumor cells release exosomes. Exosomes also contain potential tumor antigens, and APCs take up the antigen and cross present it to CD8+ T cells.
(D) Immune cells, such as NK cells, CD8+ T cells, and DCs, may also be heated and become activated.

Immunologic effects of hyperthermia

- Innate immunity refers to the cells and the proteins that are present in the body and are ready to fight diseases at all times; the cells of adaptive immunity are only called to action if pathogens overcome the power of innate immunity.
- Immune system players:
  - Cytokines - a large group of proteins that are secreted by specific cells of immune system; they are a category of signaling molecules that mediate and regulate immunity, inflammation and hematopoiesis.
  - NK - natural killer cell, part of the innate system, stimulated by HSPs.
  - CD8+ T cells – adaptive system.
  - APC – antigen-presenting cell, example: DC - dendrite cell (act as messenger between innate and adaptive systems).

Immunologic effects of hyperthermia

- Heating tumors can elicit anti-tumor immune responses by
  (1) tumor cells stimulation of the immune system through expression of surface signaling molecules and release of HSPs and/or exosomes.
  (2) directly activating intra-tumoral immune cells such as NK cells, CD8+ T cells, and DCs, and
  (3) improving immune-cell trafficking between the tumor and lymphoid organs (tumor-specific resistance against re-challenge was also observed – possibly a temperature range for immune stimulation).
Immunologic effects of hyperthermia

- Current evidence includes:
  1. Enhanced immogenicity and HSP expression seen after tumor cells are heated
  2. Thermally enhanced immune effector cell activation and function, and
  3. Thermally enhanced vascular perfusion and delivery or trafficking of immune effector cells to tumors

Thermal dose

- The heat-induced cytotoxicity of tumor cells is dependent on both temperature and time.
- Assessment of thermal dose involves time-integrated temperature analysis.
- Obtaining this information in patient-specific treatments is hindered by physiologic factors, temperature non-uniformity, etc.
- Approach suggested by Sapareto and Dewey: use information from the Arrhenius plot and a concept of “cumulative equivalent minutes at 43°C” (CEM 43°C).

Clinical trials

- Clinical trials are usually completed in phases I through III (phase IV is often used by pharmaceutical companies for drugs to receive FDA approval).
- Phase I – designed to test the initial safety of a drug, device, treatment modality, or a combination
- Phase II – test efficacy, and dose-response
- Phase III – compare the proposed research drug, device, or modality with standard treatment
- Randomized trials - patients are assigned to a particular treatment by some random mechanism
- Prospective (interventional or observational) studies vs retrospective

Phase III clinical trials: hyperthermia in enhancing radiation therapy

- An early Radiation Therapy Oncology Group (RTOG) phase III trial that included patients with various types of superficial tumors yielded well-publicized disappointing results in the late 1980s:
  - Showed only a modest benefit of addition of heat
  - Only in patients with tumors that were less than 3 cm
- It was quickly realized that the ability to actually heat tumors and monitor the temperature adequately varied enormously from center to center
- By now at least 10 randomized clinical trials demonstrated clear benefits of hyperthermia as adjuvant treatment.
Phase III clinical trials: hyperthermia in enhancing radiation therapy

- Example 1: patients with locally advanced pelvic tumors; done by a Dutch group, which tested the use of radiation alone versus radiation and hyperthermia
  - All tumors showed improved response, but most of the benefit appeared in patient with cervical carcinoma:
    - The complete response (CR) rate following RT+HT was 83% compared with 57% after RT alone.
    - Three-year survival was 27% in the RT-alone group of cervix cancer patients, 51% in the RT+HT group (p=0.003)
    - More recent (2008-2009) long-term following continues to demonstrate significant survival benefit in the patients who received hyperthermia
  - Recent development: addition of cisplatin to RT+HT

Phase III clinical trials: hyperthermia in enhancing radiation therapy

- Example 2: Recurrence of breast cancer in chest wall; combined results of 7 separate trials
  - Demonstrated significant improvements in patients receiving HT+RT vs. RT-only group
    - CR of 67% in HT+RT group vs. 31% in RT-alone
  - The greatest effect was observed in patients with lesions in areas that had previously been irradiated, thus limiting the ability of those patients to receive optimal subsequent irradiation

Phase III clinical trials: hyperthermia in enhancing radiation therapy

- Example 3: Superficial malignancies (mostly recurrence of breast cancer in chest wall); single institution prospective trial by Jones et al.
  - For the first time tumors were evaluated for “heatability” prior to randomization
  - CR of 66% in HT+RT group vs. 42% in RT-alone
  - Again, previously irradiated patients had the greatest benefit, showing a 68.2% response rate in the HT+RT group vs. 23.5% in the RT-alone group

Phase III clinical trials: hyperthermia in enhancing radiation therapy

- Example 4: Head and neck cancer; conducted by Valdagni et al.; patients with advanced stages; evaluated both primary site and neck nodes
  - Patients in stage III receiving RT+HT had a 58% CR compared with 20% in the RT group
  - Similarly, patients with stage IV disease achieved a CR of 38% compared with 7% for those receiving RT alone
  - In a separate trial by the same group metastatic cervical lymph nodes in patients with advanced local regional squamous cell carcinoma were heated:
    - The CR rate was 83% for RT+HT versus 41 % for radiation alone
    - 5-year survival was 0 for RT alone and 53% in the RT+HT group

Phase III clinical trials: hyperthermia in enhancing radiation therapy

- Example 5: Glioblastoma multiforme; conducted by Sneed et al. at UC SF; evaluated interstitial HT in combination with brachytherapy implants
  - Even in this rapidly progressing type of cancer, both times to tumor progression and 2-year survival were significantly improved for patients who received HT compared with those treated with brachytherapy alone (31% vs. 15%)
  - However, toxicity appeared to be slightly greater in patients who received hyperthermia

GBM - a fast-growing glioma that develops from star-shaped glial cells, median survival rate of ~15 months; 5-year survival rate of ~4%
Phase III clinical trials: hyperthermia in enhancing radiation therapy

- Enhancement of efficacy of both radiation and chemotherapy by heating is likely to involve overlapping mechanisms.
- In vitro data reveal the potential for enhanced chemosensitization for several chemotherapeutic agents by increased temperature, even of only 1 to 2°C.
- Hypoxic cell sensitizer have been shown to synergize with heat.

Clinical trials: hyperthermia in combination with chemotherapy

- Example 1: Esophageal cancer – two randomized studies by Sugimachi at al.
  - Preoperative CT+HT vs. CT+HT+RT
    - CRs and pathologic responses significantly improved in trimodality arm
  - Preoperative CT alone vs. CT+HT
    - Significant improvement in histopathologic response: 19 vs. 41%
Phase III clinical trials: hyperthermia in combination with chemotherapy

- Example 2: High-risk soft tissue sarcoma – randomized trials by Issels et al.
- Heating the tumor and the surrounding area (i.e., deep regional or part-body heating at a range between 40° to 43° C) during chemotherapy can significantly improve tumor control, including those in the extremities
- Demonstrated that non-uniform heating (varied 1 to 3°C across the tumor) can very successful

Hyperthermia with chemotherapy: thermosensitive liposomes

Phase III trial in patients with high-risk sarcomas: (B) Kaplan-Meier estimates of local progression-free survival, (C) disease-free survival, (D) overall survival in all patients randomly allocated treatment, and (E) overall survival in the per-protocol-induction population.

Liposomes, sphere-shaped artificially created vesicles consisting of one or more phospholipid bilayers, were first described in the mid-60s.

Hyperthermia with chemotherapy: thermosensitive liposomes

- Isolated limb perfusion technique aims to avoid amputation of limb containing bulky tumors or multiple small tumors
- Regional drug concentration can be increased 15 to 25 times compared to systemic administration
- Temperature is kept at only 39 to 40°C to avoid toxicities
- Therapy approved in Europe
Methods of producing hyperthermia

- Almost all local heating is currently delivered by
  - Microwave (100-MHz to 3-GHz)
  - Radiofrequency (500-kHz to 15-MHz)
  - Ultrasound (300-kHz to 2-MHz)
- Other techniques are either little used or in the developmental stage: radiofrequency inductively coupled, ferromagnetic seeds and nanoparticles, lasers

Methods of producing hyperthermia

- Several approaches to whole body hyperthermia
- Thermal conduction (surface heating): heated circulating water suits, heating blankets, and hot wax baths
- Extracorporeal induction: induced by heating blood during extracorporeal circulation (for example, venous perfusion WBH)
- Radiant heat or microwave radiation: the power absorption patterns are nonuniform, but redistribution of the thermal energy is rapid via the circulatory system

Clinical thermometry

- A major limitation of hyperthermia is the lack of detailed information available to guide hyperthermia
- Thus far use invasive thermometry is the standard
- A number of non-invasive thermometry techniques are under investigation to allow improved patient comfort and control of temperature distributions:
  - Infrared thermography
  - Fiberoptic sensors
  - Computed tomography, and magnetic resonance thermal imaging (MRTI)

Tumor ablation

- Tumors are heated for short intervals at high temperatures between 50° and 100° C to thermally 'ablate' nodules
- At 50°C, it takes a few minutes to kill cells; above 60°C it takes only seconds
- There are now clinical trials in place in which thermal ablation is being combined with more traditional applications of hyperthermia to improve drug delivery through the use of thermosensitive liposomes at the margins of ablated tumors

Summary

- Hyperthermia has both additive and sensitizing effects in combination with radiation therapy
- Several phase III randomized clinical trials have demonstrated a clear and significant benefits of HT as adjuvant therapy
- With more understanding of biological mechanisms, as well as improved methods of heating and temperature monitoring, it should be possible to increase clinical TER values up to 2-4 (observable in animal tumors)