HYPERTHERMIA

F. K. Storm
UCLA School of Medicine

Introduction

The use of heat in cancer treatment dates back to the ancients with the application of red-hot irons by Ramajama (2000 B.C.), Hipprocrates (400 B.C.) and Galen (200 A.D.). In more recent times, Westermark (1898) placed hot-water circulating cisterns into advanced carcinomas of the uterus and found palliative shedding of some tumors. Coley (1927) introduced "toxin" therapy for cancer, but stated that responses were associated with temperatures of 39-40° for several days duration, suggesting that the febrile reaction might have been the tumoricidal agent. Simultaneously Keating-Hart and Doyen (1910) introduced electrocoagulation of tumors, which is still in use today. Warren (1933) was one of the first to apply infrared and high-frequency current heating of tumors and found objective remissions of some cancers. With the subsequent development and popularity of x-irradiation therapy, hyperthermia research was all but abandoned until modern times when the selective thermosensitivity of tumor cells was more fully appreciated.

Modern Concepts of Low-Temperature Hyperthermia

Selective Thermosensitivity of Cancer Cells

At temperatures between 41-45°C (106-113°F), cancer cells are slightly more sensitive to heat than their normal cell counterparts. In vitro and in vivo tumor models have shown irreversible damage and complete regression of various tumors at 42-45°C, while normal cells were killed at at least one degree higher temperature of more than double the duration of heating.[1-4]

Mechanism of Action

Hyperthermia causes alteration in both DNA and RNA synthesis, as well as depression of multiple cellular enzymatic systems required for cell metabolism and division. Its major model of action may be to increase cell and lysosome membrane permeability, causing selective internal destruction of the cancer cell. Less-well oxygenated cells seem to be most vulnerable to thermic injury.

Histologic Tissue Alteration

Heat causes progressive necrosis of tumor cells at these temperatures but not in stromal or vascular cells within tumors, nor in normal surrounding tissues.[5] Autolytic disintegration of heat damaged cells is followed by a marked increase in connective tissue stroma and scar formation.[6] Interestingly, this occurs in tissue cultures of tumor-derived and tumor-producing cells, but not in normal and non-tumor producing cells. When a cell subline derived from a non-tumor-producing line acquires high tumor-producing ability, it also acquires greater thermosensitivity. Thus, the acquisition of malignant potential, both in vivo and in vitro, is accompanied by decreased thermotolerance.[7-9]

Hyperthermia Instrumention

Hyperthermia has been applied by various means, including fluid immersion and irrigation, regional perfusion with heated fluids and by electromagnetic radiofrequency waves.

All frequencies of radiofrequency waves appear to cause tissue heating by a similar mechanism. Energy is transferred into tissue by field interaction which causes oscillation of ions in the tissue or changes in the magnetic orientation of molecules which is locally converted into heat. The energy of a short-wave or microwave quantum is only about 10^{-5}eV and is therefore insufficient to produce ionization or excitation. The biological effects of radiofrequency waves are primarily and possibly solely due to heat production. However, the absorption and penetration characteristics of electromagnetic waves are markedly dependent upon tissue composition and interfaces (viz. skin, musle/fat/bone). Moreover, the depth of penetration is often limited. Incident energy absorption is a function of tissue resistance, such that tissues with high values (skin, subcutaneous tissue, bone) preferentially absorb heat in an amount 10-150 times greater than tissue with low values (muscle, organs, tumors). Therefore, if skin or subcutaneous tissue must be penetrated to heat deeper tissue, a high and potentially dangerous degree of surface energy deposition would be necessary to deep heat effectively. Satisfactory heating is presently limited to depths of 2-3 cm with commercially available diathermy apparatus. In an attempt to overcome limited penetration, several investigators have designed specialized equipment in the 915 MHz and 2450 MHz microwave bands; however even with surface cooling, documented temperatures of only 42-44°C have been possible at only 2-3 cm depth, with a continuously decreasing thermal gradient with increasing depth. For this reason, clinical trails using standard microwave techniques have been limited to superficial tumors. In an attempt to produce deep internal hyperthermia, several unique approaches have been used, particularly limb perfusion, total body hyperthermia and combination therapies.

Isolated Limb Perfusion

Cavaliere, in 1967, performed regional limb perfusions with pre-warmed blood at 41.5-43.5°C in 22 patients with large, recurrent or single metastatic cancers localized to the extremity. All gross tumor disappeared in 10 patients, 5 had regression, 3 failed to respond and 4 were not evaluable. The complication rate was high with 6 deaths and 3 immediate amputations, however, massive tumor necrosis was demonstrated.[4]

Total Body Hyperthermia

Pettigrew, in 1974, reported on 38 terminal cancer cases treated by total body hyperthermia at 41.8°C for an average of 4 hours applied by immersion in molten wax. An objective response, weight gain or pain relief plus measured tumor regression or histologic evidence of necrosis, was seen in 18/38 cases, with 4 patients dying from disseminated intravascular coagulation.[10] Larkin and Edwards, in 1976, reported

their experience with total body hyperthermia applied by a water-circulating suit. Nineteen patients were maintained at 41.5-42.5°C for 2-5 hours with an objective tumor reponse noted in 70%. Complications included one death, transient cardiac arrhythmias in 15% superficial burns in 15% and transient respiratory distress in 11%, which have been attributed to the 7-8 hours of anesthesia time required to raise and maintain body temperature in these critically ill patients.[11]

Thermoradiotherapy

Rationale. Hyperthermia has been combined with radiation therapy in the hopes of producing a synergistic and augmented response. Several investigators have concluded that hypoxic cells may be at least as sensitive to hyperthermia as are aerobic cells, forming the rationale for combined therapy since hypoxic cells are more radio-resistant than are aerobic cells.[12] Others have suggested that the primary effect of hyperthermia is to inhibit cellular recovery from sublethal radiation damage.[13]

In Vitro Studies. Tumor cells exposed to hyperthermia followed by 600 rads. radiation has resulted in a 3-log increase in cell killing comparing survival at 37°C to 43°C. Clinical doses for local and regional treatment with radiation plus hyperthermia may lie in the range of 200-600 rads/fraction.[14]

Clinical Trials. Kim, in 1977, reported his experience using hyperthermia and radiation for cutaneous cancers in man. With fractionated doses of 800-2400 rads. followed by 43.5°C surface heating by water-bath or microwaves, 7/10 patients showed significant prolonged benefits by combination therapy when compared to radiation alone.[15] Hornback has treated 70 patients with advanced malignancy with a combination of microwave (heating) and standard radiation. Of 21 patients who received a full course of therapy, 16 (80%) had complete regression of all local tumor and 9 of these remained free of disease from 9-14 months.[16] The Radiation Therapy Oncology Group has recently established a controlled study among 14 institutions to explore the efficiency of such combined therapy. Phase 1 studies suggest that effective thermal doses are probably in the range of 43-45°C, combined with higher doses of radiation equivalent to 4,000 rads. in four weeks.[17]

Thermochemotherapy

Rationale. The combination of hyperthermia and chemotherapy has been investigated since heat is thought to alter tumor cell membrane permeability and enhance uptake of chemotherapeutic agents.

In Vitro Studies. In 1970, Giovanelia found a 4-log kill in leukemia cells at 42°C in 3 hours. However, a 100-fold kill enhancement was observed with the addition of Dihydroxybutylaldehyde, with no increase in toxicity. DL-glyceralydehyde, melphalan, sodium oxyamate, and actinomycin-D were also active in combination with heat.[18] In vitro data also suggests benefit using hyperthermia with adriamycin.[19] In 1976, Goss reported the survival of four human fibroblast strains and seven melanoma cell lines after exposure to various concentrations of melphalan alone and in combination with heat at 42°C for 4 hours. He found that combined treatment was not only synergistic but increased the differential between fibroblast and melanoma lines. [20]

Clinical Trials. In the treatment of locally recurrent and intransit melanoma of the extremities using hyperthermic limb perfusion, Stehlin found an increased response from 35% to 80% by the addition of heat (41°C) to melphalan perfusion.[21]

Modern Cencepts of High-Temperature Local Tumor Hyperthermia

Rationale of Selective Local Hyperthermia

Most studies so far have dealt with moderate hyperthermia in the range of 42-43°C, alone or in combination with x-irradiation or chemotherapy, based upon the evidence of selective thermal sensitivity of tumor cells. Lethal temperature/exposure time relationships have been established for many cells lines. However, several investigators have found that at temperatures approaching 45°C, a linear kill takes place due to progressive and irreversible protein denaturation. At such high temperatures the differential susceptibility between malignant cells and normal cells decreases and host tolerance becomes the prime consideration.[1,4,7] Therapeutic hyperthermia in this higher temperature range was not thought feasible until the realization that some solid tumors might act as a heat reservoir and retain heat due to abnormal vascularity and relatively poor blood flow. Shibata and MacLean evaluated cancers in man and found the blood supply to be poorer in all tumors studied.[23] LeVeen found that tumor blood flow was only 2-15% that of surrounding tissue using isotope dilution techniques and concluded that tumors retain more heat than normal tissue whose adaptive vasculature allows heat dissipation.[24]

Toxicity Tests of Localized Hyperthermia

Our evaluation of thermal tolerance on animal skin, extremities and viscera suported the safety of temperatures of <45°C.[25] Interestingly, when animal normal muscle reaches 43-44°C, spontaneous cooling occurs which maintains the tissue well below its thermal tolerance limit. This phenomenon has been observed by others and supports the theory of normal tissue physiologic adaptation to hyperthermia, and is consistent with augmented blood flow.[24] When external radio frequency hyperthermia is applied to canine normal viscera, no selective heating of any normal organ occurs.

Animal Tumor Investigations

Using shortwave induced hyperthermia, Dickson reported that 7/10 rabbits bearing VX2 carcinoma had complete tumor regression with cure of the host. The temperature of skin and normal muscle remained 3-4°C lower than minimal tumortemperature and no injury occurred.[25] In our experience hypertheria applied to spontaneously arising dog tumors results in solid tumor heating above 45°C, with normal adjacent tissues remaining at physiologic temperatures. Moreover, at treatment termination, effectively heated tumors disspitate heat much more slowly than do adjacent normal muscle, which shows that normal tissues and tumors have different capacity to dissipate incident heat.

Human Clinical Trails

LeVeen applied shortwave hyperthermia to 21 patients and achieved tumor temperatures over 46°C in each case, 8-10°C higher than adjacent normal tissue. Tumor necrosis or substantial regression of cancer was noted in each case with minimal destruction of

normal tissue. However, he found that for internal tumors, energy was best transmitted to surgically exposed lesions to avoid heating and occasional burns of surface tissues, as others have experienced.[24]

Our development of specialized radio frequency instrumentation that produces hyperthermia to any depth without preferential surface tissue heating has allowed further clinical investigation of both superficial and deep internal solid tumors.[25-27]

In 30 patients with 36 refractory cancers, we found that intratumor temperatures of 42-50°C could be achieved in more than three-fourths, with virtually no normal tissue injury. Selective hyperthermia was possible with both primary and metastatic solid tumors, and appeared to be independent of tumor histology. Intratumor heating above 45°C was achieved most often in tumors ≥ 5 cm. in diameter. Most of the tumors that could not be heated to 45°C displayed physiologic adaptation to heat, similar to adjacent normal tissues. While standard methods of cancer therapy (surgery, x-irradiation, chemotherapy) are most effective for small tumors, our data suggest that hyperthermia may be uniquely effective against larger tumors. Tumor necrosis was marked in lesions heated ≥ 50°C for 15-60 min. on one or more occasions. Such treatment caused rapid coagulative necrosis and vascular thrombosis. Superficial tumors generally would slough within several days of therapy, however, effectively heated visceral tumors would remain intact with little change in size, with no evidence of systemic tumor breakdown products by serum creatinine, urate or urinary protein determination. Serial biopsies of these internal tumors revealed few functional vessels and progressive tumor replacement of scar. All superficial normal tissues and viscera that were evaluated had the capacity to adapt to heat and, with proper radio frequency application, could be maintained within a physiologically safe temperature range.[25-28]

Hyperthermic Immune Enhancement

Several investigators have suggested that selective tumor regression after hyperthermia may, in part, be due to some augmentation of the immune systems. Few studies are available. Goldenberg found growth inhibitation of human colonic tumors growing in hamster cheek pouches after shortwave diathermy heating, as well as growth inhibitation of contralateral, presumably normothermic cheek pouch tumors.[22] Hahn found that sarcomas implanted in mice were highly sensitive to cure by radio frequency heating. However, cell-kill as assessed by cloning efficiency of treated and immediately excised tumors was insufficient to account for the in vivo cures. This suggested that delayed killing might be the result of stimulation of a tumor-directed immune response, secondary to the direct effects of low or high dose hyperthermia.

Future Prospectives

The results of animal research and initial clinical trials, associated with our development of safe and effective equipment, indicate that hyperthermia may become a potentially useful form of local cancer therapy when fully evaluated. Clinical trials are now underway to determine the most therapeutic dose/time regimen, and to determine toxicity and therapeutic enhancement ratios of combined chemotherapy and x-irradiation with hyperthermia, as well as any changes in the hose immune system with such therapies.

Patients with advanced cancer which is refractory to standard methods of therapy, or who have cancers where no standard therapy exists, are candidates for experimental hyperthermic therapy.

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