Hyperthermia in the Treatment of Cancer

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Introduction

Cancer cells, unlike normal cells, exhibit growth whereby sensitivity to normal controlling factors has been completely or partially lost.[11] Treatment is directed towards eliminating these cancerous cells by exposure to cytotoxic agents.

Most recently hyperthermia has been added to the list of cytotoxic therapies for treatment of cancer which also includes radiation, chemotherapy, and surgery. Although heat by itself is cytotoxic, hyperthermia is used most often as an adjunct to other types of treatment. The use of an extracorporeal circuit may provide a method of heating blood and perfusing a tumor, a region, or the whole body to a level that may be toxic to cancer cells but not to normal tissue. An awareness of the principles of hyperthermic cancer therapy, as it may apply to the patient undergoing hyperthermic extracorporeal circulation, is beneficial to the understanding of cancer therapy.

History

Evidence of the use of heat and caustic agents in treating small non-ulcerating cancers was obtained from translations of Ramajama (2000 B.C.), Hippocrates (400 B.C.), and Galen (200 A.D.)[2]. Accounts of spontaneous tumor regressions following illness with lasting high fever such as smallpox, influenza, tuberculosis, and malaria were further supported in the late 1800's by documented evidence of disappearance of verified sarcomas following infection with erysipelas. Subsequently, Coley began treatments of malignant tumors with febrile therapy using mixed toxins of erysipelas to obtain several years of disease-free survival in one-third of inoperable carcinomas and sarcomas treated. Coley stressed the importance of maintaining the fever for several days at 39-40 °C for effective treatment.

The use of water-circulating cisterns and high frequency currents was followed by the technique of electromagnetic heating, called diathermy, as a more refined method to deliver heat locally to target tissue. Results published in 1974 by Pettigrew and associates demonstrated whole body hyperthermia to be a safe and reliable technique for the treatment of cancer.[4]

Basic Principles

Heat itself is damaging to cells. Thermal damage is dependent on both the temperature applied and the duration of exposure. The goal of hyperthermic therapy is to achieve cytotoxic temperatures in the tumor for a sufficient length of time without damaging the surrounding normal tissue. The rate at which blood flows through any given area of tissue determines the amount of heat that may be carried away and therefore is a major determinant of the temperature rise in that tissue.[7] In normal tissue, heat will cause vasodilation (Fig. 1). In a tumor, the microvasculature is made up of an overabundance of capillary beds which are unable to dilate. Blood flow through the tumor is more sluggish, thus unable to dissipate heat applied to the area. The inability to respond to heat by dilation as normal vasculature would, also subjects the tumor to hypoxia, anaerobic metabolism and local acidosis; these conditions in turn make the tumor tissue more vulnerable to thermal injury.[6] A description of microvascular pathology after heat treatment of tumors showed microvascular thrombosis presumably due to endothelial damage of the tumor capillaries.[16]

There is some indication of an enhanced cytotoxic effect with the combined use of heat and chemotherapeutic drugs; however, it is not clear if this effect is differentially cytotoxic to tumors compared with normal tissue.[1] It is known that the activity of many drugs

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Presented at AmSECT's Third National Symposium on Thermal Regulation, August 27-29, 1984, Boston, MA

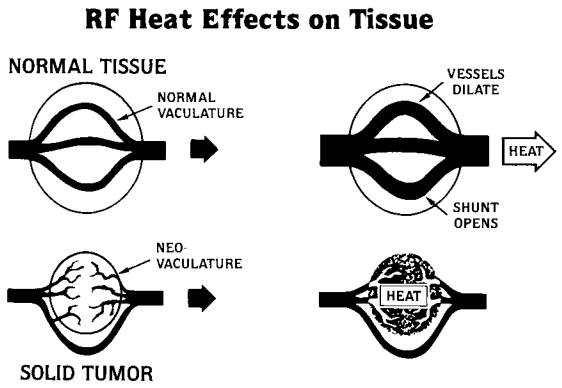

Figure 1: Heat Effects on Tissue

increases with heat, that drugs which are not active at normal temperatures may become more efficient at 42 °C, and a cell's ability to repair lethal damage is inhibited with heating.[8] Herman and associates demonstrated that the cytotoxicity of hyperthermia alone or together with some chemotherapeutic drugs may be diminished by slow rates of heating.[21]

Synergism has been demonstrated between hyperthermia and ionizing radiation. Results have shown greater cytotoxicity with combination of these devices than with the additive effects of each. Heat potentiates the effect of radiation therapy by inhibiting the cell's recovery from sublethal radiation damage.[9]

The amplified cytotoxic action due to combination of heat and chemotherapeutic drugs and radiation can be partially explained by examining the effect of each therapy on parts of the replication cycle of cells. (Fig. 2) The cell cycle of cancer cell is similar to that of normal cells. Each cell begins its growth during G1 phase where enzymes necessary for DNA production, other proteins, and RNA are produced. S-phase follows as the time of DNA synthesis. When DNA synthesis is

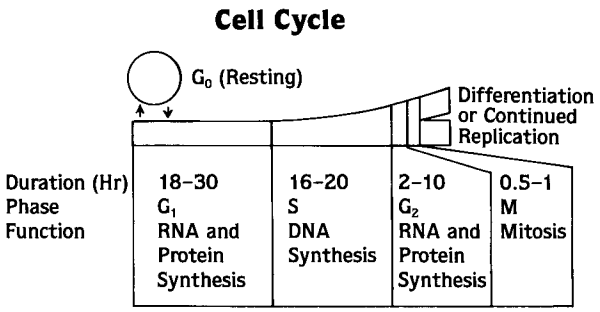

Figure 2: Cell Cycle
Manual of Cancer Chemotherapy, Roland T. Skeel, M.D., Editor, Copyright 1982, p. 5. Used with permission of Little, Brown and Company, Boston, MA.

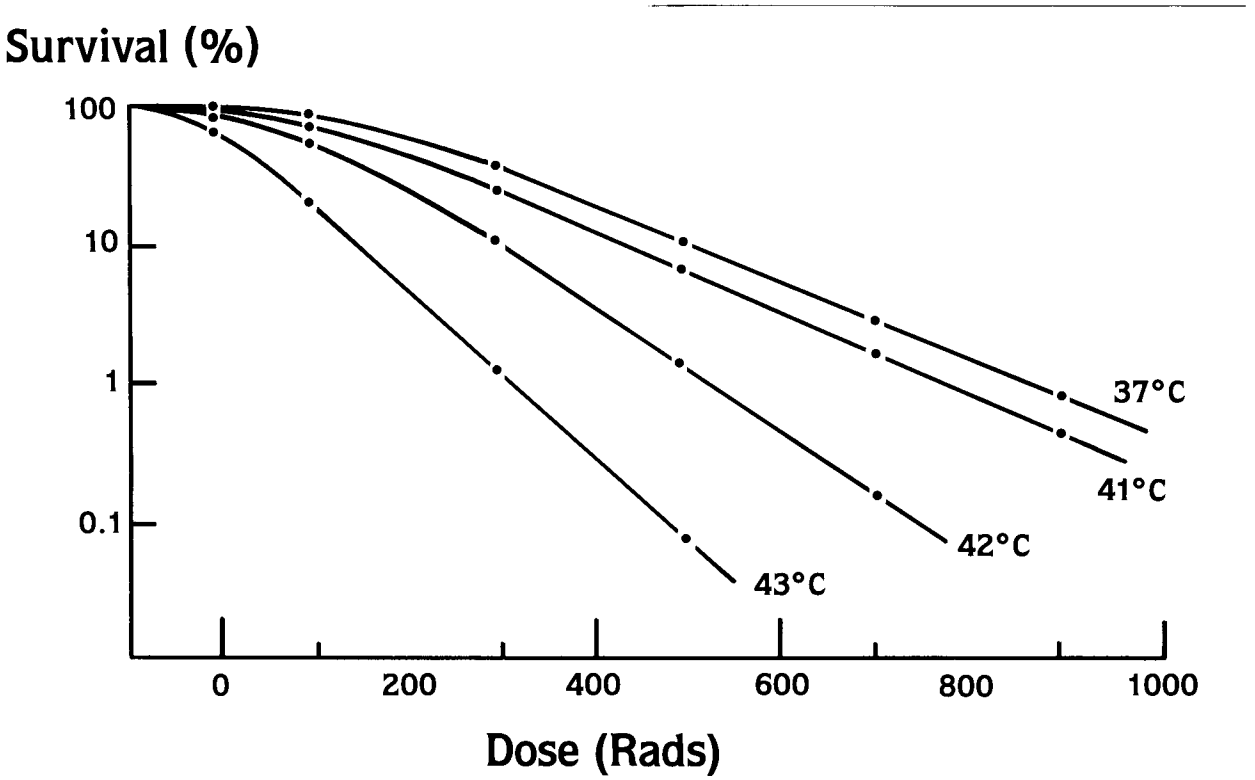

Figure 3: Percent Cell Survival vs. Dose (Rads) at Various Temperatures
"Basic Principles in Hyperthermic Tumor Therapy," F. Dietzel, *Recent Results in Cancer Research—Vascular Perfusion in Cancer Therapy*, Schwemmle Vol. 86, 1983.
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complete, the cell enters G2 (premitotic period) during which more protein and RNA synthesis occur. The G2 phase is followed immediately by M-phase (mitosis) when cell division actually takes place. Each of the newly formed cells enters G1. The G1-phase is in equlibrium with a resting state called Go. Cells in Go-phase are relatively inactive with respect to syntheses and so are insensitive to many chemotherapeutic agents.

Certain drugs, however, show specificity in their mechanism of cytotoxic action such that the cell is more susceptible to drug damage at given times in this replication cycle. Heat shows greatest effect during S-phase and M-phase, while cells are more susceptible to radiation damage during G1-phase.[3] The asynchronous combination of these susceptible times enhances the chance of affecting more cells for a given exposure. For example, beneficial effects can be obtained with intermediate doses of radiation (2000-4000 rads) when combined with hyperthermia. (Fig. 3) This is of great value to a patient unable to tolerate higher doses because of the cumulative effect of previous courses of radiation.[2]

Regional (Local) and Total Body Hyperthermia

Hyperthermia treatment techniques can be categorized as two types based on site of involvement: local (regional) and whole body.

Local hyperthermia involves externally applied heating by microwave, radio-frequency and ultra-sound or internally applied heat by extracorporeal perfusion of isolated sites. Microwave or radio-frequency sources (2450 MHz microwaves to 500 KHz long wave diathermy) can be directed locally by insertion of needle guides or implants into the tumor, whereas ultrasound can be focused and is better able to penetrate body mass to reach deep-seated tumors.

The regional extracorporeal technique involves isolating the target site from the systemic circulation with tourniquets so that this area may be perfused with a high concentration of anticancer drug at high temperatures while avoiding systemic toxicity and leakage of concentrated drug to the rest of the body. Local hyperthermia permits perfusion of given areas with drugs of greater concentration and exposure to higher temperatures than can be tolerated systemically.

Whereas local therapy may be used in isolated tumor sites, metastatic disease requires a systemic approach.[1] Whole body hyperthermia techniques include immersion of the body in molten wax, hot water or hot air, thermally controlled water circulating suits or blankets and extracorporeal circuits.

Hyperthermia is of clinical interest primarily in the temperature range of 40-43 °C.[5] Whole body hyperthermia in humans is physiologically limited because the rate of complications increase exponentially above 42 °C.[5] Because of the narrow margin between the effective temperatures to treat cancer cells and that of increasing complications resulting from high levels of heat, it is imperative that temperature monitoring be done from sites which will most accurately reflect the temperature of the tissues throughout the body. The temperature measurement site will be influenced by the site of heat application.

In some modes of heating, particular areas of the body receive more heat than other areas resulting in burns. Areas susceptible to burns may include cannulation sites used for extracorporeal circulation, skin when in contact with hot wax, hot air or hot water, and cutaneous sites at pressure points such as the heels and buttocks in contact with water blankets. In a cancer patient, burns may become a serious complication when the patient's resistance to infection is suppressed by chemotherapy, radiation, or malignant disease.[17]

Particular structures can tolerate temperatures up to 45 °C without cell damage while systemically the limit is probably not more than 43 °C for 12 hours.[13] Skin, esophageal, pulmonary artery, rectal and bladder temperatures are the sites most often monitored. Skin probes are superficial by comparison, therefore more greatly influenced by non core body temperature factors. The induction of hyperthermia places the body in a condition of quickly changing temperatures which need to be monitored closely and accurately. Rectal temperature often lags behind other measured values because of its location influenced by massive abdominal viscera. Rectal temperature may be used for a comparison temperature but not as the only index of total body temperature. Bladder temperature, measured by a thermistor tipped Foley catheter may be most accurate if one considers that urine transferred to the bladder comes from the kidneys which receive a substantial amount of flow from the extracorporeal system.

Benzinger[15] discussed the use of the tympanic membrane as a site of measurement based on its agreement with hypothalamic temperature and arterial blood temperature enroute from the heart to the brain. There is, however, a great amount of discomfort and risk of

damage to the membrane when a probe must rest against it. The esophageal measurement site has been strongly advocated[14] as most meaningful in quickly changing thermal conditions since it serves as the best available index of aortic arch blood temperature. This choice is based on the thought that the heart and lungs function as a thermal mixer with the aortic arch temperature being most representative to changes in heat production and loss of the body.[13] If a Swan-Ganz thermodilution catheter is used, monitoring of pulmonary artery temperatures becomes available as a site of measurement reflecting intracardiac blood temperature.

Clinical Experiences

Regional hyperthermic perfusion was reported to be an effective treatment of melanoma and sarcoma by Cavaliere in 1967.[20] Most recently it has been shown that hyperthermic perfusion can further improve the prognosis for patients with malignant melanoma of the limbs.[18]

Certain factors may be responsible for better results seen with regional hyperthermia therapy as compared to results seen with systemic therapy. Patients selected for regional hyperthermic perfusion present isolated tumor sites in contrast to systemic tumor involvement seen in patients requiring whole body therapy. Regional perfusion permits isolated sites to be exposed to higher temperatures and greater drug concentrations without systemic toxicity. These factors contribute to regional perfusion being less systemically traumatic than whole body therapy. In addition, more clinical experience has been gained in regional perfusion methods than in systemic therapy.

Whole body hyperthermia was first documented as a safe method in 1974.[4] Since then several methods of inducing systemic hyperthermia have evolved. In 1979, Parks and associates documented treatment of advanced malignancy of extra-corporeal hyperthermia.[17]

Systemic hyperthermia places additional stresses on many systems of the body primarily the cardiovascular system which becomes a limiting factor to intensity of therapy. In order to avoid severe hypotension, good left ventircular function is needed to increase the cardiac output in response to heat induced vasodilation.[19] A review of literature reveals that at hyperthermic (41-42 °C) conditions, heart rate increases to 150-170 beats per minute, mean arterial pressure and pulmonary capillary wedge pressure decrease, and cardiac index increases. Cardiac arrhythmias rarely occur. Several groups have reported cases of patients with apparently nonsymptomatic mitral valve prolapse,not previously detected. These patients developed symptoms with induction of hyperthermia which included hypotension and reduced cardiac output requiring termination of heat treatment.[26] The proposed mechanism for this observation was a failure to maintain adequate diastolic filing and therefore a failure to maintain stroke volume as heart rate increased in response to heat.

In whole body hyperthermia, anticoagulation therapy is imperative and requires some particular considerations. Anticoagulation is kept at adequate minimal doses. Suggested safe clotting times are 3.5 to 4 times baseline activated clotting time. In consideration of previously discussed possible mechanisms of thermal injury, since there is a vascular clotting response to heat which increases damage to tumor masses it may be of value to minimize anticoagulation.[17] Hyperthermia and its tendency to increase the utilization of heparin, combined with the minimal dose guideline for anticoagulation, requires extremely close monitoring of clotting times. Frequent addition of heparin to the extracorporeal circuit is common.

The catabolic effect of previous anticancer therapy and the nature of the disease process may place the patient in need of plasma protein replacement. Albumin is the primary component of the plasma proteins[22] of the blood. It contributes approximately 62% of total protein concentration and 70% of total colloid osmotic pressure. Albumin may be used as the protein oncotic portion of the prime or replacement fluid during therapy. Herman[21] documents that severe generalized edema (anasarca) was found to be more prominent in patients whose fluid replacement consisted of a high volume of crystalloid as opposed to patients who were pretreated with colloid solutions and then given smaller amounts of crystalloid during treatment. This observation occurred irrespective of method of hyperthermia treatment (extracorporeal or warm water blanket) or maximum temeprature reached. Herman found the occurrence of pulmonary edema was less frequent and less severe when use of colloid, lower volumes of cyrstalloid, and positive end expiratory pressure (5-10 cm of H_2O) was used.

In any method of hyperthermic therapy sweating causes a great amount of fluid loss from the patient.[1] As mentioned previously, as body temperature rises, systemic vasodilation occurs increasing volume uptake by the patient. These factors in combination with urine output and effects of anesthetic agents collectively con-

tribute to the need for volume replacement to the patient. Electrolyte studies should be monitored throughout the therapy for evidence of need for electrolyte replacement.

The choice of anesthetic technique is important for several reasons. The type of anesthesia used affects the patient's systemic pH and vascular flow to visceral organs.[23] Endotracheal respiratory gas anesthesia may permit a more normal or acidic pH,[4,24,25] while intravenous sedative and spontaneous respiration produces a more alkalotic pH.[1] The safety of this latter technique is based on heat being a potent ventilatory stimulant which increases both tidal volume and respiratory rate. The level of narcotic and barbiturate is titrated to maintain reasonable arterial oxygen saturation and carbon dioxide elimination.[26]

A series of hyperthermic perfusions was carried out at our institution utilizing extracorporeal circulation. Thirteen patients received a total of fourteen hyperthermia treatments for a variety of malignant carcinomas. (Table 1) Two types of hyperthermia techniques were used: whole body and peritoneal hyperthermia. Anesthesia was by Ethrane or Halothane, oxygen and endotracheal respiratory control. In all cases patient temperatures were monitored by esophageal and rectal probes with maximum temperature attained at 41.5 °C rectally. At no time was the inflow (or arterial) temperature permitted to exceed 43 °C.

Although literature review of the results of other groups shows little problem with life threatening cardiovascular collapse, we designed an extracorporeal circuit which would be able to sustain a patient on cardiopulmonary bypass if needed. The system consisted of Cobe Optiflo II[a] oxygenator with integral cardiotomy reservoir through which we maintained 1.5 liters of oxygen to preserve oxygenating function

a Cobe Laboratories, Lakewood, CO 80245

Table 1
Table of Hyperthermia Treatments

Pt	Sex	Age	Tumor	Site of Disease	Peritoneal / WBH	Rectal Temp / Time	Drug	Date of Treatment	Result
1	F		Ovarian Carcinoma	Omentum	Peritoneal	N/A	N/A	3-80	↓ 5-80
2	F	61	Ovarian Carcinoma		Peritoneal	N/A	cis-Platinum	6-80	↓ 2-81
3	F	59	Breast	Bone	WBH	41.5 2 hrs	none	8-27-81	↓ 5-83
4	M	26	Hodgkins	Stage IV	WBH	41.5 2 hrs	none	10-8-81	↓ 3-9-82
5	M	29	Malignant Melanoma	Systemic	WBH	41.5 1 hr	DTIC 1500 mg	11-12-81	↓ 2-14-82
6	F	41	Ovarian	Intra-Abdominal	Peritoneal	41.5 2 hrs	none	11-17-81	↓ 5-24-82
7	M	33	Kaposi's Sarcoma	Systemic	WBH	41.5 1.5 hrs	none	2-16-82	
8	F	52	Ovarian Adeno-Carcinoma	Liver & Peritoneum	WBH	41.5 1 hr	cis-Platinum 100 mg	3-4-82	↓ 5-6-82
9	F	50	Colon Carcinoma	Ovaries	Peritoneal	41.5 1 hr	cis-Platinum 100 mg	4-22-82	↓ see 13
10	F	56	Renal Carcinoma	Lung	WBH	41.5 1.5 hrs	none	5-17-82	↓ 3-7-83
11	F	45	Ovarian	Pelvis	Peritoneal	41.5 1 hr	cis-Platinum 100 mg	10-29-82	N/A
12	F	26	Mycosis Fungoides	Systemic	WBH	41.5 1.5 hrs	none	12-14-82	↓ 1-25-83
13	F	50	Colon Carcinoma	Ovaries	WBH	41.5 1 hr	5-FU 1 g cis-Platinum 50 mg	1-13-83	↓ 4-20-83
14	F	27	Ovarian Carcinoma	Colon & Liver	WBH	41.5 1 hr	cis-Platinum 50 mg	3-17-83	↓ 6-3-83

↓ = expired

should it be needed. The arterial pump used was a Bio-Medicus Biopump[b] and arterial filtration with Pall Adult arterial blood filter[c]. Arterial (inflow) and venous (outflow) temperatures were monitored by use of an electronic digital thermometer. Pressures and inflow resistances were monitored at the arterial (inflow) side of the circuit.

The whole body hyperthermia method included heparinization with 3 mg/kg of porcine intenstinal mucosca heparin and initiated through cannulations of femoral arterial and venous sites. Prime varied according to patient requirements as to proportions of albumin (75 g), packed red cells (if needed), lactated Ringers, heparin 10,000 units. Flows were directed towards achieving a cardiac index flow of 2.4 liters/min/meter^2 until maximum temperature was reached at which time the flow was reduced to 2.0 liters/min/meter^2. Activated clotting times using the Hemochron method were repeated at 15 minute intervals unless conditions required monitoring more closely. Protamine was given following termination of extracorporeal circulation.

Peritoneal hyperthermia involves cannulation of opposite sides of the peritoneal cavity providing an inflow and outflow site for warm perfusate which consisted of 2000 ml of lactated Ringers solution. Flows generally ranged from 1-2 liters/minute as consistent with outflow return. Careful monitoring is needed to avoid obstruction to peritoneal outflow and subsequent inflow pressure increase.

Lab values monitored before, during, and after therapy included CBC, CEA, SMA-12, and arterial blood gases. CEA (carcinoembryonic antigen) is used to monitor response to therapy.

When drugs were added to the circuit, they were administered when maximum desired temperature was achieved, and circulated for the prescribed time. Following systemic hyperthermia, blood from the circuit was infused as needed following termination of extracorporeal circulation. Following peritoneal hyperthermia, the perfusate was drained from the peritoneal cavity of the patient. The peritoneum was then irrigated with large amounts of normal saline solution. Patients were passively allowed to return to normal body temperature in the following hours of recovery room observation.

Results of these hyperthermia treatments were consistent with other groups' findings showing partial remission in treated patients. No deaths occurred as a result of these hyperthermia treatments.

b Bio-Medicus, Minneapolis, MN 55344
c Pall Biomedical Products, East Hills, NY 11548

Future

Results of regional and whole body hyperthermia show therapeutic value. Regional hyperthermia for many reasons has shown greater prospect. Whole body hyperthermia involves a much more complex system in itself and exposes the patient to greater systemic physiologic stress.

Many topics in regard to hyperthermic treatment for cancer need to be studied. One major difficulty in research of this subject is that no suitable animal model has been found which has similar temperature tolerances and response of humans.[3] Pharmacologic studies may include what drugs are effective and how are their actions modified at high temperatures. What temperature levels are safe yet effective and at what duration of exposure. Continued studies need to be done in the areas of sequencing hyperthermia with other anticancer treatments and how these treatments affect its toxicity to the patient.

More recently research has shown that bacteria and their toxins directly damage cancer cells and inhibit metastases.[27] Although reminiscent of effective therapy by Coley using toxin innoculations in the late 1800's, the therapeutic value contributed by the individual components of heat, bacterial products, and the immune system response in tumor regression have yet to be defined.[3]

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