Hyperthermia Therapy

Hyperthermia is one of the most powerful anticancer, antiviral, and antibacterial therapies available, yet it is underutilized and largely unknown in North America. Hyperthermia treatment involves raising the temperature of the whole body, or of local areas of the body to 39 to 43 degrees C (102 F to 109 F). Research has shown that high temperatures stimulate cellular immunity and can damage cancer cells, usually with minimal injury to normal tissues.[1, 2, 3, 4, 5] By damaging proteins and structures within cancer cells, hyperthermia may shrink tumors.[6] In general, malignant cells are more sensitive to heat than are normal cells in the range of 41-45°C. In addition, most clinically apparent tumors (above 1-cm diameter) have blood perfusion rates less than 1/5 that of surrounding normal tissue, meaning that they may be preferentially heated. In Europe, hyperthermia is considered the 4th major modality of cancer therapy along with surgery, chemotherapy, and radiation. And in Europe, hyperthermia is often utilized as an adjunctive therapy with various conventional cancer treatments, such as chemotherapy and radiotherapy, but in some clinics, is also used alongside biological regulatory therapies.[7] As hyperthermia is non-myelosuppressive and can potentiate the tumoricidal effects of biological regulatory therapies, its use as part of a multimodality treatment approach is attractive. The positive results of randomized trials have established hyperthermia alone, or in combination with biological regulatory therapies, as an effective clinical modality for the treatment of cancer.

Temperature is a highly conserved and important parameter in all living systems. In mammalians, particularly in humans, a narrow range of 37.0 – 37.5 °C is attempted to be maintained by regulation. In this range, the complicated cellular and physiological processes are working most efficiently. Under stress conditions, e.g. infectious diseases, fever is a reaction of the organism to better handle the external

attacks. Hence, fever is a natural defense reaction of the human body. The immune system's defense cells work best at a temperature above 39 degrees Celsius (102 F.). At this temperature, all metabolic and detoxification processes are intensely stimulated. This helps overcome infections, inflammations and pain much quicker and more effectively. During fever, the build-up of perspiration activates the excretion of toxic substances. This purifies the body and improves metabolism and after the fever subsides, the body relaxes, and the pain disappears.

The following are complementary effects of fever:

- Increase in blood circulation and oxygenation of tissues
- Acceleration of metabolism, detoxification, and excretion processes
- Relaxation of muscle tension
- Increased stimulus conduction of nerve fibers
- Stimulation of cellular immune defenses
- Inactivation of chronic bacteria and viruses

Hyperthermia treatment may be local (tumor only), regional (e.g., a limb), or whole body. Physical techniques for hyperthermia include metabolic heat containment, conduction through the skin (e.g., hot water bath), perfusion of externally heated blood, heated intravenous fluids and anesthetic gases, ultrasound, and electro-magnetic EM coupling modalities. Thermometric requirements vary with the treatment modality and clinical situation. Until the late 1990s, the use of radiant whole-body hyperthermia (WBHT) was restricted to a few specialized treatment centers worldwide. During the last decade, a larger number of WBHT-devices were put into operation, particularly in Germany. Worldwide, hyperthermia is becoming more utilized clinically, due to the substantial technical improvements made in achieving selected increase of temperatures in

superficial and deep-seated tumors. In North America, however, it is rarely used, and then only as part of an alternative cancer treatment protocol or research project.

History of Hyperthermia

Fever as the imminent sign of infectious diseases has been used as a diagnostic indicator since ancient times. The effectiveness of heat as a therapy against disease is believed to be known since 3000 B.C.[8] Parmenides, a Greek physician and philosopher 2500 years ago said, “Give me a chance to create a fever and I will cure any disease.” Fever is one of the body’s best defensive and healing forces, created and sustained for the purpose of restoring health. Belief in the curative effect of fever was also shared by Celsus, a Roman author of the first systematic treatise on medicine "De Medicina," and Rufus of Ephesus, a Greek physician who lived at the turn of the 1st and 2nd century. Celsus described the hot baths as a tool in the treatment of various diseases.

There has been a historic, cross-cultural recognition of the benefit of fever and heat therapy. The healing effect of heat was first mentioned in the early civilizations of ancient Egypt, where baths in hot desert sand were prescribed for the ill. Doctors of ancient Greece started using this therapeutic approach and named it “overheating” (in Greek: hyperthermia). Other examples are the Roman sulfur hot baths, Finnish saunas, Japanese hot baths, Native American sweat lodges, and the many therapeutic hot springs in Europe, Iceland and in the Americas. Saunas and hot baths do not significantly increase core body temperature enough to have an anti-cancerous effect, but they have been shown to stimulate the immune system. More technologically innovative approaches have developed that increase core temperature or local temperature of tumor tissue to levels that damage or destroy cancer cells.

Bacteria Induced Fever Therapy - William Coley and Coley's Toxins

The history of bacteria induced fever therapy (fever induction therapy) began in the mid-19th century by several European physicians. One of the first papers on hyperthermia was published in 1866 by a German surgeon Carl D. W. Busch. He described the case of a 43-year-old woman with advanced sarcoma on her face. After the tumor was removed, the patient fell ill with erysipelas. The disease induced high temperature which led to tumor regression for over two years. Busch's discovery was fundamental because it was the first reported case showing that high temperature can selectively kill cancerous cells while not affecting normal cells.[9] Along that time others reported that cancer patients who experienced a feverish period after surgery survived significantly longer than patients without fever. In 1882, Fehleisen discovered the erysipelas causative organism as *Streptococcus pyogenes*. He inoculated these live bacteria to seven cancer patients and achieved complete remission in 3 cases.[10] In the second half of the 19th century, the practice of infectious febrile therapy was quite common not only in Germany and France, but also in Russia, and it was used to treat a wide range of diseases.

The American surgeon William Coley (1862-1936) also observed that cancer patients often recovered from their cancer if they had suffered a severe post-surgical infection of the wound accompanied by high fever. Coley developed the theory that it was the fever from the infection which had helped patients to recover from their cancer. So, he began to treat patients by injecting a *Streptococcus pyogenes* directly into inoperable tumors. He found the treatment was most effective when it provoked a fever and a full-blown infection. This led physicians to understand that the increase in body temperature not only mobilized the body's own immune system, thus fighting off the infection, but also destroyed the tumor at the same time.

Later Dr. Coley decided to use a mixture of dead *Streptococcus pyogenes* and dead *Serratia marcescens* bacteria. This was subsequently termed "Coley's Toxin". In 1893, the first patient to receive Coley's Toxin was John Ficken, a sixteen-year-old boy with a

massive abdominal tumor. Every few days, Coley injected this bacterium directly into the tumor mass and produced the symptoms of an infectious disease, but did not produce the disease itself. On each injection, there was a dramatic rise in body temperature and chills. The tumor gradually diminished in size, and after four months of intensive treatment, the tumor was a fifth its original size. Later that year the remains of the growth were barely perceptible.[11] The boy received no further anticancer treatment and remained in good health until he died of a heart attack 26 years later.

Over the next 40 years, as head of the Bone Tumor Service at Memorial Hospital in New York, Coley injected more than 1000 cancer patients with bacteria or bacterial products. By the end of his career, Coley had written over 150 papers on this subject.[12, 13, 14] Coley mainly used his toxins on patients with inoperable bone and soft-tissue sarcomas, observing that this treatment was less effective on other types of cancer such as melanomas and carcinomas. Beginning in 1899, Parke Davis and Company had begun to prepare the Coley's Toxins, so they were available for all physicians. They were widely used for the next 30 years.

In the first half of the 20th century, different formulas of Coley's Toxins were manufactured by several drug companies in the U.S. These formulations were used to treat patients with a variety of types of cancer until the early 1950s, when other forms of cancer treatment became more widely used, such as radiotherapy. Despite his reported positive results, Coley's Toxin came under a great deal of criticism because many doctors did not *believe* it possible. Medicine has always been, and still is, ruled by belief.

Additional controversies surrounding Coley's work reflect the field of oncology struggling to stabilize its understanding of how to treat cancer. For example, James Ewing, perhaps the most famous cancer pathologist in the country, was a leading opponent of Coley's work. This was a problem for Coley because Ewing was Medical Director of Memorial Hospital, and for many years was Coley's boss. Their memos to one another reflect constant interpersonal animosity. Ewing himself had become a fanatical

supporter of radiation therapy for the treatment of all bone tumors and repudiated any other theories for the treatment of cancer. Ewing therefore refused Coley permission to use his toxins at Memorial Hospital. This was ironic, because Coley had more experience than any other surgeon in the country in treating the small round blue cell sarcoma that still carries Ewing's name.

Skepticism and criticism, along with the development of radiation therapy and chemotherapy, caused Coley's Toxin to gradually disappear from use in the U.S. By 1952, the Parke Davis Company no longer produced Coley's Toxin, and, in 1962 the FDA refused to acknowledge Coley's Toxin as a proven drug.[15] Thus, in 1962 it became illegal to use Coley's Toxin for the treatment of cancer in the United States. In Europe, Australia and Asia, however, bacteria-induced hyperthermia continued in certain medical circles, and has become an advanced immunotherapy. In retrospect, William Coley's intuitions were correct. Using fever induction therapy to stimulate the immune system is effective in treating cancer. Coley was a model of the clinician-scientist, treating patients and using his practice to initiate research and build theories. But he was a man before his time, and he met with severe criticism.

During the second half of the 20th century, characterized by the heavy use of antibiotics, fever was regarded by mainstream medicine as an unnecessary, weakening state which should be suppressed or prevented. The situation today has not changed much. The immune system is constantly repressed with anti-microbials and even mild fever is suppressed with anti-febriles.

The Modern Development of Hyperthermia

Fever induction therapy today involves the injection of specific bacterial lysates, which induce the release of cytokines, and bring about a fever reaction. The immunological response of cytokine release with underlying fever has been extensively researched over the last several decades. Direct endogenous pyrogens, or proteins that produce fever, are associated with IL-1alpha, IL-1beta, TNF-alpha, TNF-beta (lymphotoxin-

alpha), IL-6, macrophage inflammatory protein 1, and IFN-alpha.[16, 17, 18] Indirect fever inducers are considered to be IL-2 and IFN-gamma.[19] Most fever response usually only reaches a maximum of around 39°C (102°F), which is not sufficient to induce enough thermal damage within cancerous tissue. However, the immunological effect of this treatment can greatly improve the general condition of the patient through stimulating the immunity, resulting in a positive response.[20, 21]

Within the last century, hyperthermia has been shown to be of great use in treating cancer. Such techniques as immersion in heated water, artificial fever production by toxins, and fever cabinets have been used historically. In September 1965, the physicist and cancer researcher Manfred von Ardenne (1907-1997) presented in the Heidelberg Cancer Research Centre the concept of his so-called systemic Cancer Multistep Therapy - a combined modality treatment including whole-body hyperthermia. At the time, whole-body hyperthermia was attained by a warm water bath plus induced hyperglycemia and a high dosage application of oxygen. Since hyperthermia treatment was a very strenuous procedure, Ardenne supplied oxygen to the patients in support of the treatment. At first he had difficulty optimizing the treatment, since there was no way to exactly control the internal temperature of the body.[22] Dr. von Ardenne was the first person to specifically treat cancer patients with the help of hyperthermia by using long-wave infrared light. Over the years, however, more technologically advanced equipment guaranteed better control of the overheating process and made widespread use of hyperthermia in clinics possible.

Types of External Hyperthermia

To reach the temperatures necessary to disrupt cancer cell growth, today externally induced hyperthermia procedures are used. These involve ultrasound, microwave, radio wave technology, or by infrared light. This differs from induced fever therapy, by which body temperature increase is induced with a bacterial protein. The high-tech science of external hyperthermia has greatly evolved in the precise control of the therapeutic application of heat. Numerous devices have now been developed to produce elevated

temperatures of the body, by a variety of physical means. After a shift in focus to local and regional hyperthermia, there is now a resurgence of interest in systemic hyperthermia or whole-body hyperthermia (WBHT) for treatment of cancer as well as other systemic diseases.

Apart from the induction of biological fever by pathogens or toxins, all methods of external hyperthermia involve transfer of heat into the body from an external energy source. The administration of a hyperthermia treatment requires technology to heat the tissues as well as technology to monitor, control and evaluate the thermal or other parameters involved in the heat treatment. External hyperthermia is basically divided into three types: local hyperthermia, regional hyperthermia and whole-body hyperthermia.[23, 24] Because of the different routes and different range of heating temperature, the treatment scopes are also different. Local hyperthermia is appropriate for small tumors, such as breast, whereas, the regional and whole-body variant is used for metastatic tumors.

Local hyperthermia is performed with superficial applicators (microwave, radio wave, ultrasound) of different kinds (waveguide, spiral, current sheet etc.). These applicators are positioned upon superficial tumors coupled to the tissue by water bags or a water bolus. The penetration depth depends on the frequency and size of the applicator, and typically the clinical range is not more than 3 – 4 cm. A system for local hyperthermia consists of a generator, the control computer, the applicator and the possibility to measure temperature in the tumor. Then the power is increased until the desired temperature is achieved. Indications for local hyperthermia include chest wall recurrences, superficial malignant melanoma lesions, lymph node metastases of head and neck tumors.

Local hyperthermia is further typed as External, Endoluminal, and Interstitial. Local external approaches are used to treat tumors that are in or just below the skin. External applicators are positioned around or near the appropriate region, and energy is focused on the tumor to raise its temperature. Intraluminal or endocavitary methods may be

used to treat tumors within or near body cavities, such as the esophagus or rectum. Probes are placed inside the cavity and inserted into the tumor to deliver energy and heat the area directly. Based on their design the interstitial hyperthermia techniques can be categorized in four groups; radiofrequency, microwave, hot source and ultrasound techniques. The hot source techniques distinguish themselves from the other techniques because the tissue is heated by thermal conduction while the other techniques deposit energy directly in the tissue at a distance from the heating source.

Endoluminal hyperthermia uses natural orifices to position various kinds of endocavitary applicators (microwave, radio wave, ultrasound) in direct contact to a tumor. A counter electrode might be positioned on the body surface to steer the power deposition pattern. By physical reasons, the penetration depth around those endoluminal applicators is limited and of the order of the applicator´s diameter (in the cm-range). Accessible tumors include esophageal carcinoma, prostate carcinoma, rectal and cervical carcinoma.

Interstitial techniques are used to treat tumors deep within the body, such as brain tumors. This technique allows the tumor to be heated to higher temperatures than external techniques. Under anesthesia, probes or needles are inserted into the tumor. Imaging techniques, such as ultrasound or magnetic resonance, may be used to make sure the probe is properly positioned within the tumor. The heat source is then inserted into the probe. For interstitial hyperthermia, an array of interstitial antennas (microwave) or electrodes (radio wave) is implanted in accessible tumors which might be located in deep or superficial tissues. The distance between the antennas must not exceed 1 – 2 cm, and therefore lesions with diameters below 5 cm are suitable (in order to limit the number of puncturing tracks). Interstitial hyperthermia is an invasive procedure. Temperature measurements must be performed at the antennas and between them. In most systems, every single antenna is controlled by its own generator. Dedicated systems have in addition two or more segments per antenna or electrode controlled in phase and/or amplitude. Clinically interstitial hyperthermia has been applied for prostate carcinoma, recurrent breast cancer and malignant brain tumors.

Thermoablation may also be performed with thin laser applicators (laser induced thermotherapy or LITT) and is considered a minimally invasive procedure. The applicators must be implanted in the lesions under computer tomography or magnetic resonance guidance. Achieved temperatures are high (up to 90 °C), but the thermal gradients are quite steep and the effective range is 1 – 2 cm (i.e. lesions with diameters of 3 – 4 cm are the limit using standard techniques). Liver metastases (number up to 4) are probably the most treated condition with LITT.

Another form of local hyperthermia that is growing in popularity, especially in China, is high intensity focused ultrasound (HIFU). HIFU is a hyperthermia procedure that applies precise high-intensity focused ultrasound energy to heat to destroy cancerous and diseased tissue through ablation. When magnetic resonance imaging is used for guidance, the technique is sometimes called magnetic resonance-guided focused ultrasound, often shortened to MRgFUS or MRgHIFU. Magnetic resonance imaging guidance allows the tumor to be visualized and targeted, and in addition provides a means to measure tissue temperatures in real time. HIFU is used often as a solo treatment or sometime used with other treatments. Unlike radiotherapy, HIFU is a non-invasive technique that also leaves healthy tissue next to a tumor undamaged. In China, over the last decade, thousands of patients with breast cancer, liver cancer, pancreatic cancer, bone tumors, renal cancer, prostate cancer and uterine fibroids have been treated with ultrasound imaging-guided HIFU.

In the U.S., HIFU is only approved treat uterine fibroids. However, there is ongoing research in the area of breast cancer with HIFU conducted by Dennis L. Parker, PhD, a professor of Radiology at the University of Utah and Director of the Utah Center for Advanced Imaging Research (UCAIR). Dr. Parker and colleagues at UCAIR are leading in the development of a HIFU system for breast tumors. Now in prototype form, their system has been tested on phantoms and samples. According to Dr. Parker, "From the standpoint of something that could ultimately be used to treat breast cancer, I think this is an excellent, potential device. The advantage of HIFU for breast cancer is that it's

totally noninvasive. It has the opportunity eventually to totally eradicate the disease without any surgical intervention at all."[25]

In regional hyperthermia, interference patterns in deep seated tumors of the pelvis or lower extremities are generated by an array of phase-controlled antennas radiating in the range of 70 – 150 MHz These antennas are surrounding the whole circumference of the cross section, i.e. all possible directions are employed to deposit power into the target volume. The higher the number of antennas (and the higher the frequency), the better the potential to control the patterns. In particular, several rings of antennas in direction of the patient axis are useful to enable the flexibility with respect to the anatomical structures for optimization. A current frequency of clinical interest is 100 MHz. Locally advanced and/or recurrent tumors of the pelvis are the major indications for regional hyperthermia, i.e. rectal carcinoma, cervical carcinoma, bladder carcinoma, prostate carcinoma, or soft tissue sarcoma.

In contrast to local or regional hyperthermia which heats only one part of the body, namely where the tumor mass is located, whole body hyperthermia (WBHT) heats the entire body. WBHT heats the whole body either up to 42 °C for 60 - 120 minutes (so-called extreme WBHT), or only 39.5 – 41 °C for longer time, e.g. 3 hours (so-called moderate WBHT). Temperature and duration of treatment is usually individually determined depending on the patient's health condition. Between the heating and cooling phase, the entire procedure may last about 4 to 5 hours. Generally, WBHT in the treatment of metastatic cancer raise the patient's temperature to 41.6° C. to 41.8° C for 60 to 90 minutes. This is much higher temperature and longer plateau than the WBHT IRB[26] research protocols used in the U.S.

For WBHT, the patient is as far as possible thermally isolated, and infra-red radiation with different ranges of wavelengths (for several available systems) is depositing energy in the superficial tissues of the body until the desired temperature is achieved. For extreme WBHT, 60 – 120 minutes are needed until the patient has 42 °C achieved under general anesthesia (plus/minus intubation). For moderate WBHT, often deep

sedation is sufficient. In any case, careful monitoring of the systemic parameters are required for any kind of WBHT and an intensive care unit should be available in the background.

WBHT is used principally in advanced stages of cancer and as a metastatic prophylaxis in high risk patients, e.g., young premenopausal women with breast cancer, lymph node involvement and negative hormone receptor status. Up to now, several WBHT-approaches have proved to be safe and associated with acceptable toxicity rates when radiant heat devices are employed. Until the late 1990s, the use of WBHT was restricted to a few specialized treatment centers worldwide. During the last 20 years, a larger number of WBHT-devices have been put into operation throughout Europe and Asia. Because many women diagnosed with invasive breast cancer have undetected occult metastases at the time of their primary tumor diagnosis it may be more desirable to employ WBHT as opposed to local hyperthermia.

In Europe and Asia there are several types of WBHT systems in clinical use. Over the last decade, patient warming with infrared radiation has been established as a standard procedure for WBHT treatment. WBHT systems differ with regard to the spectrum of infrared radiation used and the area of application (front or back of the patient). At the time of this writing some of the more common systems are the Heckel HT-3000[27], the Oncotherm WBH-2000[28], the Chinese manufactured Gamma Star GMX-RL-03 WBH system, and the Ballya International Ltd WBH system, only to name a few. The Heckel HT-3000 (Manufactured by: Hydrosun Medizintechnik GmbH, Esslingen, Germany), uses water-filtered infrared radiation (wIRA) delivered by four wIRA emitters to the chest, and two heating elements for warming the air under the tent-like canopy. It features continuous measurement of core temperature, heart rate, oxygen saturation, blood pressure, ECG, respiratory frequency. The OncoTherm WBH-2000 unit is a chamber that encloses all but the patient s head. Special light-emitting diode (LED) radiators deliver computer-generated, alloyfiltered IRA wave-lengths that penetrate the skin to deliver heat to the capillary bed. The manufacturer claims that these wave-lengths also preferentially stimulate the immune system.

Hyperthermia Societies

Much of the history and development of hyperthermia is rooted in Europe, and has been fostered by organizations such as the European Society for Hyperthermia Oncology.[29] China and Japan have also become world leaders in the clinical use of hyperthermia. In 1978, research on hyperthermia in Japan was started by the Hyperthermia Study Group. Six years later, the Japanese Society of Hyperthermic Oncology (JSHO) was established. Since then hundreds of research articles have been published in China and Japan. It is estimated that more than two hundred hyperthermia units are in use across Japan. Compared to other countries, Japan has the highest number of hyperthermia equipment installed, and the most doctors involved in hyperthermia therapy. The main reasons for the advanced state of hyperthermia research in Japan include the development of excellent heating equipment, high membership in JSHO, grant-in-aid by the Japanese government, and coverage by insurance for this form of therapy.30

In 1981, the North American Hyperthermia Society was founded by those who shared the opinion that hyperthermia continued to show promise as a therapeutic modality, and that the growing numbers of investigators and the amount of data produced required a separate forum for discussion of results and planning future directions of research and application. In 1985 the North American Hyperthermia Society, together with the European Society for Hyperthermic Oncology, and the Japanese Society of Hyperthermic Oncology cooperatively founded the International Journal of Hyperthermia and adopted it as their official journal.[31]

Despite several decades of ongoing usage in Europe, China and Japan, and numerous human studies, WBHT is still considered ‘experimental’ in the U.S. where chemical medicine trumps all other forms of oncological therapy. Hence, WBHT is limited to a few research IRBs (institutional review board) in the U.S. However, numerous clinics abroad, especially in Germany, Austria, Italy, Switzerland, China and Japan, regularly use WBHT as an integrative approach for cancer care.

Hyperthermia Anticancerous Mechanisms

Understanding of the mechanisms by which heat destroys cancer cells is ever changing. Partly because is a new emerging field, and the biological effects of local hyperthermia and WBHT, or systemic hyperthermia, are different. Aside from the stimulation to the immune system, hyperthermia has a unique physiological effect on tumors. It was initially thought that tumor cells have intrinsically higher heat sensitivity than normal cells, but this is now shown to be not universally true. Although some neoplastic cells are more sensitive to heat than normal cells, this appears to be more the case for local hyperthermia than the lower temperatures used in WBHT. However, as we have seen in oxidative therapy, tumors do have their weaknesses, and heat definitely can disrupt the tumorous environment. Contrary to healthy tissue, tumors cannot easily divert heat because of their primitive blood supply. This has to do with the fact that tumor cells have a different metabolism and their vascular supply network is different compared to those of healthy cells. Because of their poorly constructed vasculature, tumors have poor perfusion, thus heat dissipation by convection is reduced. At high temperatures (43.8 C and up) tumors become a heat reservoir with a consequent rise in temperature, which if maintained for too long damages their microcirculation and further impairs convective heat loss. Also increased fibrinogen deposition at damaged sites in the vascular wall leads to occlusion of tumor microvessels. Significant heating of the tumor cells results, which may be directly cytotoxic.[32]

We know when body temperature reaches 101.3° F (38.5° C) the immune system becomes active and begins producing white cells and immune chemicals. Within hours, almost every major defense within the immune system doubles its efforts. This process appears to be dormant in many cancer patients, who typically report never having experienced a fever in a long time. Results from studies show that cancer cells form a special type of protein structure on their surface when heated to a temperature of approximately 42° C, which does not happen with normal cells. These protein

structures, also known as heat shock proteins (HSPs), are recognized by the body's immune system as foreign substances, thus enabling the immune system to destroy them.[33, 34]

The increased expression of HSPs after hyperthermia treatment has been shown to correlate with increased immunogenicity of cancer cells through their lysis by alpha/beta T cells. HSPs belong to a group of "stress proteins" secreted after a wide range of stimuli such as exogenous heat, oxidative injury, heavy metal toxicity, and microorganism toxins. HSPs have been suggested to act as 'molecular chaperones' in presenting protein structures to the lymphatic system. In this respect they may serve as carriers for antigenic tumor peptides, and thereby, increase the natural immunity to attack cancer.[35, 36]

Basically, hyperthermia works in two ways: first by creating thermal damage and secondly by stimulating the body's own immune system.[37] An overview of some specific mechanisms of hyperthermia in cancer treatment are as follows.[38]

1. Programed cell death of cancer cells (apoptosis) - The mechanisms of hyperthermia causing cancer cell apoptosis are complex, but mostly related to disrupting the vascularity of the tumor, denaturing cellular proteins, changing the fluidity of bio-membrane, leading to destruction of the cancer cell membrane, as well as cell nuclei and other cytoplasmic components.

2. Inhibiting metastasis - Hyperthermia can inhibit the synthesis and repair of cell DNA, RNA and protein to stop cancer cells' reproduction, and inhibit the gene expression and synthesis of tumor matrix metalloproteinase to inhibit the metastasis trend of tumor. Another proposed metastasis inhibiting mechanism of hyperthermia is that it can inhibit transforming growth factor beta-1-induced epithelial-mesenchymal transition in cancer cells, hence, altering the properties of metastatic potential in cancer cells and inhibit tumor metastasis.[39]

3. Inhibiting the formation of tumor blood vessels (anti-angeogenesis) - Studies have shown the WBHT can inhibit gene expression and synthesis of vascular endothelial growth factor excreted by cancer cells. This can prevent the formation of blood vessels to tumors, which destroys the basic condition for growth and development of cancer metastasis.

4. Enhancing the effect of chemotherapy - WBHT results in an increase delivery of drugs to tumor sites partly because of increased systemic blood flow. Additionally, because hyperthermia can change the permeability of cell membranes this can increases the concentration of anticancer drugs in the cancer cell cytoplasm.[40] WBHT can also increase blood vessel permeability by increasing the effective pore size between the loosely bound endothelial cells forming tumor microvessels, permitting larger molecules, such as nanoparticles and gene therapy vectors, to pass into the interstitium.[41]

5. Enhancing the effect of radiotherapy – Hypoxic cells and the cells in the S-stage are especially sensitive to heat, but resistant to radiation. Hence, hyperthermia and radiotherapy compensate each other. Hyperthermia has been shown to potentiate the effect of radiation therapy in the treatment of superficial lesions (less than 3 cm in depth).[42] Clinical experience has largely been limited to treatment of recurrent, metastatic superficial melanomas, chest wall recurrence of breast cancer and cervical lymph node metastases from head and neck cancers. Tumor depth is a critical factor when combining radiation therapy and hyperthermia. Lesions less than 3 cm from the surface treated with radiation therapy and hyperthermia have been shown to have a significantly greater complete response rate compared to the complete response rate of lesions greater than 3 cm deep.

6. Bone marrow protection - WBHT can stimulate bone marrow by increasing peripheral blood flow and can induce the differentiation of peripheral blood and hematopoietic stem cells in bone marrow. Clinical practices showed that whole-body hyperthermia will not increase marrow suppression like radiation or chemotherapy.

7. Hyperthermia improves the function of immune system - Because practically all cancer patients have a lower than average core temperature and are unable to develop

a fever they are unable to activate their immune system. Hyperthermia assist in activating several immune functions. Though the immunotherapeutic role of hyperthermia is not yet completely understood it has been shown that WBHT can activate long acting T-lymphocyte and increase the activity of T- and B-lymphocyte.[43] At treatment temperatures above 40°C, both enhancing and inhibitory effects of cytotoxic activity of NK cells against tumor cells have been reported. In particular, an enhancement of human NK cytotoxicity against tumor cell targets has been demonstrated using a temperature of 39.5 °C.[44] WBHT can also facilitate the redistribution of body's white blood cells to improve the monitoring function of body's immune system.

Though whole-body hyperthermia has primarily been used in the field of oncology, it is also used to treat an array of other illnesses. Particularly, WBHT is clinically used for certain chronic infections diseases, such as HIV[45], hepatitis C[46], herpes[47], borellia[48] (Lyme disease) and numerous other pathogens.[49] Literature supports that the retrovirus, human immunodeficiency virus (HIV), which is thought to cause acquired immunodeficiency syndrome (AIDS), is heat sensitive at temperatures which can be tolerated in humans. This heat sensitivity is true for many viruses and bacteria.

Toxicity and Side-Effects

Based on several research groups' reports, whole body hyperthermia, accompanied by suitable monitoring, does not lead to any serious or sustained organ dysfunction and can therefore be regarded as a safe therapy.[50, 51, 52, 53, 54] Bear in mind that many advanced cancer patients are debilitated, anemic, and may have poor organ function due to chemotherapy and radiotherapy. Sophisticated monitoring equipment has greatly lessened the side-effects of WBHT, but the condition of the health patient should be evaluated prior to each treatment.

Since WBHT is rarely utilized as a single treatment modality, it is important to recognize that systemic hyperthermia combined with chemotherapy and radiation and chemotherapy may enhance some of the toxicities associated with these modalities. For example, the cardiotoxicity of doxorubicin and both the renal toxicity and hematological toxicity of platinum agents may increase under hyperthermia.[55] However, non-toxic biological regulatory therapies are excellent companions to hyperthermia and minimize any risk.

Impressive effects of hyperthermia, both internally induced as fever therapy, and external applications, have been proven again and again in scientific studies. Research has shown that temperatures between 40°C and 43°C can activate immunity, damage cancer cells, and treat numerous infectious diseases with no or minimal injury to normal tissues. There currently are dozens of clinics in operation throughout the world that are using various types of hyperthermia for treatment in oncological and other conditions.

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Such boards are formally designated to approve (or reject), monitor, and review biomedical and behavioral research involving humans. They often conduct some form of risk-benefit analysis in an attempt to determine whether or not research should be completed. The alleged purpose of the IRB is to assure that appropriate steps are taken to protect the rights and welfare of humans participating as subjects in a research study.
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