Hyperthermia (HT), or thermal therapy, is the use of high temperature or heat against cancerous tissues. This article will look at local-regional HT, which has historically been used in some form or another across most ancient medical traditions. Naturopathic training includes the use of various local therapeutic heat treatments including hydrotherapy, moxibustion, herbs such as cayenne, heating pads, diathermy, and others. More recently, HT has been studied alongside radiotherapy and chemotherapy, and has been shown to act as a chemotherapy and radiotherapy sensitizer. There has also been a significant amount of literature published on the immune effects of HT, including HT’s ability to modulate cells of the innate and adaptive immune systems. By multiple mechanisms, HT treatments have been shown to significantly improve local tumour control and provide a survival advantage in many solid cancers. Some human trials published in the literature have been contradictory, largely due to differing experimental temperatures and exposure times. This article reviews the evidence available and describes various potential mechanisms of action that HT exerts on the immune system. Clinical pearls from the practice of a Fellow of the American Board of Naturopathic Oncology are provided.
Introduction

HT is a procedure whereby the temperature of cancerous tissue is increased above what is considered normal, most often in the 40-43 degrees Celsius range (Wust 2002). Through multiple mechanisms, including direct cell killing, treatments have the ability to significantly improve local tumour control and provide a survival advantage to cancer patients (Dewey 1994). HT can also act as a chemotherapy and radiation sensitizer (Jones 2003). HT can modulate directly or indirectly the cells of the innate and adaptive immune systems (Frey 2012). HT can improve tumour oxygenation, in both diffusion-limited and perfusion-limited hypoxic cells, which reverses the incapacitating effects of hypoxia in the tumour microenvironment and improves treatment outcomes (Song 2001). Finally, HT can inactivate superoxide dismutase (SOD) and allow tumours to be destroyed by inducing oxidative stress (Lehmann 2012). There are multiple forms of HT, such as whole body HT, but this paper will focus on local-regional HT. Even though HT may appear to be a promising adjunctive therapy, there have been contradictory results published in the literature. One argument is that the inconsistent outcomes after HT are due to differing experimental temperatures and exposure times (Frey 2012). The challenges in utilizing HT include heating tumours to high temperatures in a precise and reproducible manner, defining and calculating the required thermal dose for efficacy, and appropriately measuring temperature. There has been significant progress on all these issues, particularly in the last decade. This article will review the evidence available and describe various potential mechanisms of action of HT on the immune system. Clinical pearls from the practice of a Fellow of the American Board of Naturopathic Oncology will be provided.

Immune Effects of Hyperthermia

HT has general and specific effects on the innate and adaptive immune responses, similar and beyond that of fever. Studies have shown that HT has beneficial effects on macrophages. In one trial, the experimenters measured the response of macrophages to phytohaemagglutinin, a lectin that is used to measure cell-mediated immunity (Manzella 1979). It was found that even mild HT increased macrophage responsiveness. Higher temperatures, even if not above 40 degrees Celsius, can influence lymphocyte transformation and mitogenesis, both of which increase the activity of the immune system (Skeen 1983). A study that examined whole body HT in mice showed that HT influences the migration of Langerhans cells (Ostberg 2000). Langerhans cells are the dendritic cells of the skin and mucosa. As such, they are responsible for taking up microbial antigens and other antigens and acting as antigen-presenting cells. The systemic activation of the immune system by HT may help target metastatic tumour cells (von Ardenne 1972).

Heat shock proteins (HSPs) are proteins than can be induced by physiological stress, including environmental stresses and pathological states such as fever and inflammation (Morimoto 1993). They have immunomodulatory functions and can have positive and negative effects on regulating macrophage function, depending on the cellular location of the HSPs. Extracellular or membrane-bound HSPs might serve as a danger signal to stimulate the immune response (Schmitt 2007). HSPs are synthesized in response to HT treatments. In one study looking at HSP72, it was...
found to be expressed on the surface of malignant cells but not on normal cells (Multhoff 1995). HSP-expressing cells are more susceptible to lysis by natural killer (NK) cells. HSPs are released after necrosis and in turn then stimulate macrophage and dendritic cells to secrete cytokines, which can inhibit tumour development and progression (Basu 2000). HSPs may also act to repair or limit damage to otherwise healthy cells, protect them from or prevent future damage, or place the cells in a state that limits expression or fixation of damage (Tomasovic 1989). The exact mechanism is unclear.

Macrophage function can also be enhanced through an increased secretion of tumour necrosis factor (TNF), formerly known as TNF-alpha. Mild acute or chronic HT can increase tumour cell susceptibility to TNF (Tomasovic 1989). In vitro, TNF has effects on tumour vasculature and TNF-mediated cell killing is stimulated by chronic heating (Ruff 1981). Studies that have examined the effects on macrophages of potential treatment sequences have shown that appropriately constructed sequences for macrophage priming and triggering combined with HT could augment the cytotoxic actions of macrophages, which could have important clinical implications (Tomasovic 1989).

NK cells have the ability to detach from tumour cells and kill novel tumour cells (Bhat 2007). However, there is some conflicting evidence on the way HT influences them. NK cell activity is modified by their environment and seems to be impaired in various cancer types, including lymphoma, breast cancer, and multiple myeloma (Konjevic 2012). HT at temperatures above 40 degrees Celsius has been shown to decrease NK cell activity in many in vitro studies (Azocar 1982). However, whole body HT has been shown to increase NK cell activity in vivo (Zanker 1982). Despite the conflicting evidence at higher temperature ranges, there is evidence that fever-range thermal stress at a temperature of 39.5 degrees enhances NK cell cytotoxicity against tumour cells (Dayan 2008).

**Hyperthermia Trials**

Several older non-randomized trials have looked at the use of HT alone and in combination with other therapies. A review of 14 studies looking at HT by itself with 343 patients demonstrated complete response rates varying from 0-40%, with an overall complete response rate of 13% (Hetzel 1987). However, these studies found that using HT alone resulted in a short duration of response. The first two randomized studies failed to show a beneficial effect of adding HT to radiotherapy (van der Zee 2002). One criticism of these initial randomized trials was that the treatment techniques were inadequate for the patients included. Since then, many trials have examined the use of HT in conjunction with either chemotherapy, radiotherapy, or both. The large majority have shown significantly better results with the HT group (van der Zee 2002).

A review looking at selected phase I, II, and III trials investigated the effects of HT combined with radiotherapy, chemotherapy, or both, obtained data on 2200 patients (Falk 2001). The trials it analyzed had been performed in patients with a variety of solid tumours including: melanoma, head and neck cancer, breast cancer, cancer of the gastrointestinal tract or urogenital tract, glioblastoma, and sarcoma. The authors concluded that although the effects of HT vary depending on cancer type, complete response rates with HT, alone or in combination with other therapies is possible (Falk 2001).

One of the most compelling studies involved randomizing patients with metastatic stage IV squamous cell cancer of the head and neck to radiotherapy, or to radiotherapy plus HT (Overgaard 1995). In this trial, the complete response rate improved from 41% to 83%, with 5-year overall survival increasing from 0% to 53% with the addition of HT (Valdagni 1993). Another compelling study analyzed the results of five randomized controlled trials in the treatment of superficial localized breast cancer (Vernon 1996). This study included over 300 patients who had advanced primary or recurrent breast cancer and in which local radiotherapy was indicated. Not all trials demonstrated an advantage for the combined treatment, but the overall complete response rate for radiotherapy alone was 41% and for the combined treatment was 59%. The greatest effect was in patients with recurrent lesions where further irradiation was limited to low doses (Vernon 1996). Local HT appears to follow a dose-response relation, in that the number of treatments is related to the degree of local tumour control (Wust 2002). There are dose-response relationships between temperature and killing effects as well. These vary depending on cell lines and tumour types (Dewhirst 1992).
glioblastoma were randomized and treated with partial brain radiotherapy. Those patients whose tumour was still implantable after teletherapy were randomized to brachytherapy boost with or without HT for 30 minutes immediately before and afterwards. 79 patients were randomized between the two groups. Both endpoints that were measured (time to progression and survival) were significantly longer for HT than without HT, regardless of the use of brachytherapy (Sneed 1998).

HT can be utilized for many types of malignancy. In one study, patients with advanced adenocarcinoma and severely symptomatic benign prostatic hyperplasia received transrectal microwave HT of the prostate (Szmigelski 1991). Local HT was given twice a week for a total of six sessions and the treatments were administered using a water-cooled rectal applicator. Each session lasted for 30 minutes and the rectal mucosa temperature was controlled at 45 degrees Celsius. The results indicated a significant increase in NK cell cytotoxic activity in the adenocarcinoma patients, indicating a transient stimulation of cell-mediated immune reaction (Szmidielski 1991).

Finally, a more recent randomised phase 3 multicentre study investigated the use of regional HT with chemotherapy in high-risk soft-tissue sarcoma (Issels 2010). Prior to these, phase 2 studies showed that the combination of HT and chemotherapy improved local control compared to chemotherapy alone. In the phase 3 study, patients were randomly assigned to receive chemotherapy alone or combined with regional HT in addition to local therapy. 341 patients were enrolled in total, with approximately half in each group. Patients had higher progression rates and death rates with chemotherapy alone. The treatment response rate in the group that received HT was 28.8%, compared with 12.7% in the chemotherapy alone group. The adverse events associated with HT included pain, pressure, and skin burn (Issels 2010). Overall, HT appeared to improve patient outcomes and was a valuable addition to chemotherapy.

Clinical Pearls

Dr. Gurdev Parmar, ND, FABNO is the co-founder and medical director of the Integrated Health Clinic (IHC) in Fort Langley, British Columbia. Dr. Parmar has been using local-regional HT with patients since 2009 and fever-range whole body HT for the past year.

At the IHC, local-regional HT has now been used with over 250 patients, totalling over 3500 treatments. This has given Dr. Parmar and his team an opportunity to use this treatment against many different tumour types and at varying stages of disease. The IHC is finalizing a database for all patients treated thus far with HT. Dr. Parmar will be presenting the basic data from this database soon at the 41st annual International Clinical Hyperthermia Society conference in Budapest. The rest of the more detailed retrospective data is slated to be published in early 2013.

Dr. Parmar is also working on a prospective study that is moving forward. He reports having noticed a significant benefit to many of his patient’s quality of life and overall survival when adding HT to their treatment plan. He looks forward to the day that HT will be the fourth pillar of conventional oncology care, as it improves the efficacy of chemotherapy and radiotherapy without any risk of interference. It also can be used as a salvage therapy once conventional measures have been exhausted, while maintaining a good quality of life, as there are few potential side effects or risks.

Conclusion

HT is a treatment strategy whereby the temperature of cancerous tissues is increased above normal. This paper focused largely on local-regional HT. HT is best used in combination with chemotherapy and radiotherapy, and can also be utilized in the late treatment of various cancers as a standalone therapy, or as a salvage therapy. Among its various possible mechanisms of action, much research has been conducted on the stimulating effects of HT on the innate and adaptive immune systems. HT appears to stimulate the activity of macrophages, NK cells, and also has immunomodulatory functions via the creation of HSPs. Elevated temperatures influence lymphocyte transformation and mitogenesis, both of which increase the activity of the immune system. The systemic activation of the immune system by HT may help target metastatic tumour cells.

HT is an effective chemosensitizer and radiosensitizer. HT also increases the amount of oxygen in the target tissue, which makes chemotherapy and radiotherapy function more effectively. In studies where HT has been used as a standalone therapy, response rates have been varied but impressive. HT has been studied in numerous cancer types, including melanoma, head and neck cancer, breast cancer, cancer of the gastrointestinal tract or urogenital tract, glioblastoma, sarcoma, and others. It is encouraging that the large majority of the research across various cancer types demonstrates that HT is an effective oncological treatment that can improve response rates and patient survival. Clinical experience from the practice of a Fellow of the American Board of Naturopathic Oncology in the treatment of over 250 patients has mirrored these findings. Finally, the most recent and best-conducted trials have shown that HT provides benefits above and beyond conventional oncological treatment approaches with minimal side effects.
References


