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Hyperthermic Extracorporeal Applied Tumor Therapy (HEATT®) in Advanced Unresponsive Cancer

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2023 Symposium Presentation

Hyperthermic Extracorporeal Applied Tumor Therapy (HEATT®) in Advanced Unresponsive Cancer

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Abstract

Hyperthermia has been utilized for cancer therapy, including metastatic cancer, for decades with isolated success. Previous research has indicated that the elevated temperature of 42°C induces cell death, apoptosis, or senescence of responsive cancers, providing a mechanism for tumor destruction and management. Veno-venous perfusion-induced systemic hyperthermia (V-V PISH) may be the key to improving advanced tumor responsiveness to previously failed chemotherapy and/or radiation as combination therapy. The most recent iteration of V-V PISH, Hyperthermic Extracorporeal Applied Tumor Therapy (HEATT®), provides homogeneous heating of all tissues with electrolyte and pH control and continues to prove safe and effective. The utilization of (HEATT®) in advanced, unresponsive cancers should be further explored as a part of integrative oncology care.

Keywords: hyperthermia, whole-body hyperthermia, veno-venous perfusion-induced systemic hyperthermia, hyperthermic extracorporeal applied tumor therapy, metastatic cancer, naturopathic oncology, integrative oncology.

Introduction

Cancer cells are vulnerable to destruction by heat at temperatures between 41°C and 43°C, theorized due to a lack of heat shock proteins.[1-4] In contrast, this temperature range is tolerated by normal cells, allowing this unique temperature range to be utilized as a therapeutic window with minimal damage to surrounding tissues. Although conduction allows millimeters of tissue penetration for effective heat transfer during hyperthermic intraperitoneal chemotherapy (HIPEC), veno-venous perfusion-induced hyperthermia (V-V PISH) is required for homogeneous heating of all vascular beds, including that of primary and metastatic tumors. Additionally, conductive heat cannot attain the internal temperature required for the therapeutic target temperature of 42°C without sustaining significant damage to the non-neoplastic tissues. Within the tumor itself, hyperthermia causes increased blood flow, elevated glycolysis, and increased acidosis.[5] The rise in temperature of the tumor alters perfusion, which eventually induces cell death, apoptosis, or senescence in susceptible cancer cells.[6]

A recent historical review of whole-body hyperthermia using heat conduction techniques concluded that there was no improvement in quality of life or survival for patients with metastatic cancer.[6] Earlier techniques of whole-body hyperthermia therapy demonstrated identifiable morbidity and mortality.[7,8] Advances in perfusion-induced systemic hyperthermia have achieved controlled homogeneous heat distribution (42 +/- 0.2ºC for 2 hrs) with normalized blood chemistry by dialysis, detoxified blood by sorbent, and normalized pH by CO_2 removal to effect direct cancer cell kill

and apoptosis.[9-12] We will outline two decades of V-V PISH treatment development, culminating in a description of our growing clinical experience. Two phase-one clinical trials and the most recent clinical experience foreshadow potential future applications.

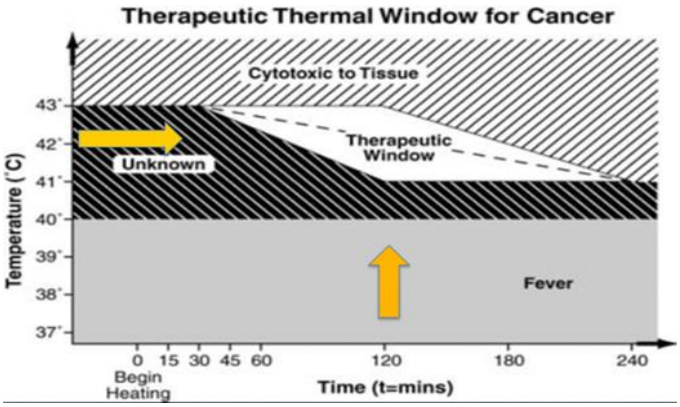

Figure 1. Therapeutic thermal window for cancer showing heat sensitive ranges for normal and susceptible cancer cells.

Presentation Summary

V-V PISH, as a modification of veno-venous ECMO, uses FDA-approved components to homogeneously raise the core body temperature to achieve a tightly controlled target temperature in both normal and cancerous tissues within the body. Under general anesthesia and systemic anticoagulation, image guidance allows insertion of 13-17 Fr cannulas in the femoral to internal jugular veno-venous configuration. Blood is then withdrawn at 20% of cardiac output, heated in an external circuit, dialyzed, charcoal filtered, and returned to the right heart to perfuse the lungs. The anatomy of the lungs allows their extensive surface area to serve as a radiator, permitting heat to be evenly distributed before being pumped to the body by the left heart.

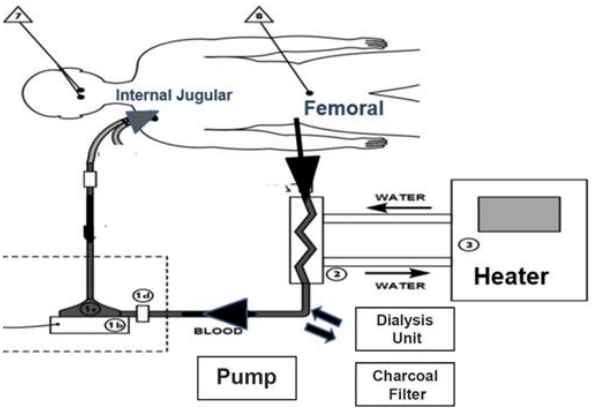

Figure 2. Basic design of HEATT® delivery system

Our first phase-one FDA clinical trial evaluated the safety of the treatment. Ten patients with unresponsive stage IV lung cancer received V-V PISH for 120 minutes and reached core body temperatures ≥ 42°C to ≤ 42.5°C.[13] The trial was void of major complications and demonstrated a statistically significant increase in median length-of-survival for hyperthermia patients. Survival from diagnosis to death was 450 days in the hyperthermia group compared to 96 days in the matched control group .[13]

VV-PISH was updated to provide more efficient dialysis and heat exchange, then rebranded as Hyperthermic Extracorporeal Applied Tumor Treatment (HEATT®). By heating the body to a tightly-controlled core body temperature of 42°+/-0.2°C HEATT® significantly increases tumor blood flow, enhances vascular permeability, and increases oxygenation.[14] This tightly-regulated temperature allows for these specific biochemical changes to facilitate maximal tumor cell destruction without permanent damage to the surrounding, non-neoplastic cells.[14] Additionally, the increase in temperature causes an increase in immune cell trafficking into the tumor, resulting in altered cytokine activity.[15, 16]

The second phase one clinical trial for HEATT® included ten patients with ovarian cancer who had failed first-line chemotherapy and surgery options, second-line chemotherapy and remained eligible for third-line therapy. The patients were treated with 1-6 cycles of HEATT® every 28 days, mimicking chemotherapy treatments that utilize the fractional cell kill hypothesis of cytotoxic agents. The mean overall survival following HEATT® was 596 days, while the historical survival was estimated at 267 days.[17] More importantly, seven of these patients received chemotherapy regimens post-HEATT®, and all responded to previously failed regimens to prevent disease progression. An FDA review on HEATT® presented "no comments or reservations."

HEATT® delivers a predictable thermal dose achieving a homogeneous distribution of heat measured by multiple designated temperature monitoring points to calculate average core body temperature for real-time feedback control.[11] This regulation prevents periods of elevated or insufficient temperature ranges as well as serum solute maintenance to further limit the risk of hemodynamic instability.[11] A series of large animal experiments confirmed this homogenous heating while maintaining electrolyte balance, demonstrating no arrhythmias or hemodynamic instability.[12,13]

Our most recent clinical experience addressed hospice-eligible patients with unresponsive, advanced cancers.[17] Thus far, 8/13 patients have exceeded the hospice-eligible predicted survival of 90 days, with 6/13 exceeding the predicted 6-month end-of-life limit and 5/13 exceeding a year.[17] These outcomes are very similar to the previous ovarian phase-one trial results, substantiating the potential therapeutic benefits of HEATT®. While there were no complications specific to the use of HEATT® fragility, age > 80, and immobility had a negative impact on HEATT®.[17] With updated criteria from these findings, four out of the five deaths before the 90-day expected hospice survival timeline would now meet exclusion criteria.[17] Absolute and relative contraindications, such as irreversible anticoagulants and angiogenesis inhibitors, are actively being revised based on a growing patient experience and follow-up.[17]

How do these concepts impact clinical practice?

Advanced, unresponsive metastatic cancer remains the leading cause of death in solid tumors.[18] Perfusion-induced systemic hyperthermia may be the key to improving advanced metastatic tumor responsiveness to previously failed chemotherapy and radiation.[17] Our innovative HEATT® technology has continued to demonstrate safety and efficacy. Utilizing HEATT® as part of a naturopathic program or an integrative oncology approach for advanced cancer treatment appears effective for advanced ovarian, breast, colon, and lung cancers, including those with metastasis. In conclusion, HEATT® could prove to be an integral component of comprehensive cancer care for patients with advanced, unresponsive cancer.

Disclosures

The system and methods of Verthermia® are protected by four issued US patents (11,065,379; 11,185,622; 11,191,883, and 11,239,551). Two other US patent applications and one international or PCT (Patent Cooperation Treaty) application are also in process. Currently, Verthermia® has two registered US trademarks, and two other US trademark applications are underway. Verthermia® has filed an application for an international trademark as well. Joseph B. Zwischenberger is the Chief Medical Officer of Verthermia. Roger Vertrees is the Chief Science Officer of Verthermia. Jan Winetz is the Chief Clinical Officer of Verthemia.

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