



Hyperthermia and its Clinical Application in Cancer Treatment

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Abstract

The objective of this paper is to describe history of hyperthermia and its clinical applications in cancer treatment. Hyperthermia is a promising approach for cancer therapy which is used to increase the temperature of body tissue by delivering heat obtained from external sources to destroy cancerous cells with minimal or no damaging healthy tissues. There are three main clinical applications of hyperthermia such as local, regional and whole body. Microwaves, radiofrequency, ultrasound, infrared and different kinds of hot sources (hot water, ferromagnetic, nanoparticles) heating approaches are used in some clinical trials. Hyperthermia is administered as an adjuvant to other cancer treatment modalities (multimodal oncological strategies). However, hyperthermia is still facing many challenges in cancer treatment. Some trials continue to use hyperthermia in combination with other novel interstitial technologies such as magnetic fluid hyperthermia and thermolabile liposomes, application of therapeutic monoclonal antibodies under hyperthermic conditions, and hyperthermia-induced gene therapy for the treatment of different cancers which have been discussed. Thus, progress of hyperthermia in clinical applications has already shown some benefits to cancer patients.

Keywords: Hyperthermia; Cancer; Clinical application

Introduction

Worldwide, cancer is a leading cause of death. Hyperthermia is a promising approach to cancer therapy (van der Zee, 2002). It is used to raise the temperature of a region of the body affected by cancer up to 41.5-43°C with minimal or no damaging of healthy tissues, using external and internal heating devices. It is applied together with conventional approaches such as radiotherapy and chemotherapy in the treatment of cancer patients. It is proposed that by killing cancer cells and damaging proteins and structures within the cells, hyperthermia may shrink tumors, making the cells more sensitive to radiation therapy (RT) or chemotherapy (American Cancer Society, 2009). The

increase of temperature, required can be achieved by various methods. Therapeutic potentials, expenditure of treatment, technical problems and evidence of effectiveness are diverse, based on the different hyperthermia approaches. There are three main clinical applications of hyperthermia such as local, regional and whole body. Results from studies on laboratory animal models and initial human clinical trials have been very promising and suggest that hyperthermia may have a vital role in future cancer treatment. This paper presents an overview of clinical and practical application of hyperthermia.

History

The application of heat to treat disease dates back to ancient times but took its modern form only in the last 20 years. In India, the clinical use of hyperthermia in the system of traditional medicine (Ayurveda) applied around 3000 years ago. It formed part of a clinical protocol developed called "Panchakarma" that was used in curative and preventive medicine. The first recorded uses of localized hyperthermia for cancer treatment appeared in the writings of Ramajama (2,000 B.C.)

Combination of hyperthermia and radiotherapy

Hyperthermia is considered to be one of the most potent radio-sensitizers (Lindner and Issels, 2011). Ionizing radiation generates free oxygen radicals which will attack the DNA of tumour cells. This is the primary mechanism of radiotherapy. In spite of the cancer cells low in oxygen and pH range or in S-phase, are relatively radio-resistant (Jones *et al.*, 2005). This is where hyperthermia may need as a supplementary for radiation therapy. Table 1 shows combination of hyperthermia and radiotherapy.

Table 1: Combination of hyperthermia and radiotherapy treatment in different types of cancer patients

Author	Year	Modality	Tumor entity	Treatment	Response
Algan	2000	Local	Prostate	Radiation	Yes
Van der Zee	2000	Regional	Cervix, rectum, Bladder, pelvic	Radiation	Yes
Harima	2001	Regional	Cervix	Radiation	Yes
Jordan	2001	Interstitial	Prostate	Radiation	Yes
Jones	2005	Local	Superficial lesions	Radiation	Yes
Vasanthan	2005	Regional	Cervix	Radiation	No
Mitsumori	2007	Local	Non-small cell lung cancer	Radiation	No
Matula	2007	Local	Prostate	Radiation	Yes
Aktas	2007	Local	Vaginal	Radiation	Yes
van der Zee	2008	Local	Vaginal	Radiation	Yes
Hulshof	2010	Regional	Esophagus	Radiation	Yes
Huilgol	2010	Intra-cavitary	Head & neck	Radiation	Yes
Hua	2011	Local	Head & neck	Radiation	Yes

Combination of hyperthermia and chemotherapy

Heat and drugs have been shown to interact synergistically in experiments and clinical. This proved that heat enhances the cell killing through direct thermal toxicity and shows thermal enhancement of drug efficacy (Issels,

2008). This is due to heat that can alter tumour cell membrane permeability for the penetration of chemotherapeutic drugs into tissues and absorption by the tumour. Table 2 shows clinical trials of hyperthermia in combination with chemotherapy that have been done in cancer patients.

Table 2: Combination of hyperthermia and chemotherapy treatment in different types of cancer patients

Author	Year	Modality	Tumor entity	Treatment	Response
Wessalowski	2003	Regional	Soft tissue sarcoma	Chemotherapy	Yes
Richel	2004	Whole body	Cervix	Chemotherapy	Yes
Issels	2010	Regional	Soft tissue sarcoma	Chemotherapy	Yes
Shen	2011	Regional	Non-small cell lung cancer	Chemotherapy	Yes

Combination of hyperthermia and surgery

Hyperthermic intraperitoneal chemotherapy (HIPEC) is a heated chemotherapy approach that is delivered directly to the abdomen during surgery. It is a very concentrated chemotherapy treatment for cancer patients. It is not like systemic chemotherapy delivery because systemic chemotherapy circulates throughout the body. However, HIPEC delivers

chemo-drugs directly to cancer cells in the abdomen. This permits for higher doses of chemotherapy treatment. Hyperthermia enhances the absorption of chemotherapy drugs by tumors and kills the microscopic cancer cells that found in the abdomen after surgery. Randomized trials on hyperthermic intraperitoneal chemotherapy (HIPEC) shown in Table 3.

Table 3: Combination of hyperthermia and surgery treatment in different types of cancer patients

Author	Year	Modality	Tumor entity	Treatment	Response
Scaringi	2008	Adjuvant HIPEC	Gastric	Surgery	Yes
Spiliotis	2008	Adjuvant HIPEC	Peritoneal	Surgery	Yes
Elias	2008	Adjuvant HIPEC	Pseudomyxoma peritoneal	Surgery	Yes
Di Giorgio	2008	Adjuvant HIPEC	Ovarian	Surgery	Yes
Verwaal	2008	Adjuvant HIPEC	Peritoneal	Surgery	Yes
Kerkar	2009	Adjuvant HIPEC	Stomach	Surgery	Yes
Helm	2009	Adjuvant HIPEC	Ovarian	Surgery	Yes
Elias	2008	Adjuvant HIPEC	Colon	Surgery	Yes
Baratti	2010	Adjuvant HIPEC	Peritoneal	Surgery	Yes

Current approaches of hyperthermia

Hyperthermia might be effective in the enhancement of anti-tumor immune responses (Overgaard *et al.*, 2009; Franckena *et al.*, 2009). Researchers found that combination hyperthermia with immunotherapy produced promising results in experiments and clinical aspects. Hyperthermia improves the immune reactivity through production of heat-shock proteins (HSPs), the activation of antigen presenting cells and changes in lymphocyte trafficking (Appenheimer *et al.*, 2005; Skitzki *et al.*, 2009). Tanaka and his group (2005) administered injection of immature dendritic cells intra-tumorally to enhance antitumor effect of hyperthermia using magnetic nanoparticles to treat melanoma.

A new generation of thermosensitive liposomes has been developed as another innovation which reliably enables the liberation of drugs into a heated tissue at predefined temperatures. Current studies describe that those technologies may largely enhance the thermal control of hyperthermia - guided drug -

targeting. Combination hyperthermia and with phase I/II trial of ThermoDox® to treat breast cancer patients was demonstrated in 2010.

Eisenberg *et al.*, 2010 investigated the combining effects of NV1066 (a recombinant herpes simplex virus-1 which is designed to specifically infect, replicate in, and lyse cancer cells) and hyperthermia in the treatment of pancreatic cancer *in vitro*. They concluded that the combination of hyperthermia and viral infection significantly increased killing of cancer cells to approximately 80% without damaging normal cells.

Conclusion

Hyperthermia is a very promising approach in cancer treatment. Although basically an old and historic approach for oncology, hyperthermia is not a well-known treatment modality among patients and scientists. On the other hand, hyperthermia is an effective approach for cancer treatment was proven in experiments and clinical studies. It shows significant positive results in clinical responses for cancer patients when used in combination with other treatment methods.

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