Hyperthermia: A Cancer Treatment Approach Worth More Attention

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Abstract

Hyperthermia is often combined with radiation therapy and chemotherapy in cancer treatment. It can also assist in cancer immunotherapy. Considering the minor side effect on normal tissues, hyperthermia could be applied repeatedly. More attention is necessary to incorporate hyperthermia in clinical cancer workflows.

Keywords: Hyperthermia, Cancer, Treatment

Hyperthermia therapy (HT) heats the body for treatments of various diseases since ancient Egyptians and China [1, 2]. Nowadays it is often used to achieve better anti-cancer effects in combination with radiation therapy and chemotherapy. It is well-known that HT could increase the sensitivity of tumor to other therapies via thermal. The mechanisms of HT in cancer treatment is still under exploring while its clinical applications keeps improving towards more precise and more personalized. There are three major hyperthermia approaches, known as local hyperthermia, regional hyperthermia, and whole-body hyperthermia.

Local hyperthermia focuses on a small area, mainly for tumors that near or on the skin or close to natural openings in the body, aiming at killing the

tumor with the minimal damage to adjacent tissues by heat generated with microwave, radiofrequency, ultrasound energy or using magnetic hyperthermia. The superficial hyperthermia applies the heat to the very surface of the body, the intraluminal hyperthermia works into the body cavities, and the interstitial hyperthermia affects deep in tissue with needles or probes. It has been confirmed that localized hyperthermia treatment over 40 °C substaining for an hour could kill the tumor. The noval technology of magnetic fluid hyperthermia (MFH) improves the hyperthermia precision a lot by magnetic nanoparticles [3]. MFH is non-invasive and not limited in depth penetration, moreover it has no ionizing radiation. The combination of magnetic particle imaging (MPI) and MFH could even avoid the side effect of nanoparticles in liver and spleen heated up by the oscillating magnetic field during the MFH treatment [4].

Regional hyperthermia heats an entire organ or limb. It could work as a preliminary therapy for radiotherapy or chemotherapy. Blood perfusion is one such method of regional hyperthermia, drawing out patient's blood and returning heated blood back to the desired part of the body usually with chemotherapy drugs simutaneously. For the tumors growing inside peritoneal cavity, heated chemotherapy drugs may be pumped into abdomine. The AMC-8 system has a favorable peritoneal heating properties that could promotes the future study of regional hyperthermia in gastric and pancreatic cancer [5].

Whole-body hyperthermia heats the entire body or besides the head in some cases by placing the patient in a hot room or chamber. It may also operate by covering the body with hot blanket or water-tubing suit, in which general anesthesia is needed while the treatment could bring temperary side effects like diarrhea, nausea, and vomiting. It is commonly used to treat metastatic cancer [6, 7].

One of the key issues in hyperthermia therapy is about the temperature range. Generally the range is preferred between 39 °C and 43 °C, while higher temperature is considered ocassionally. However, improper temperature and operation time in hyperthermia might lead to surface burn, tissue damaging, blood clots, bleeding and cardiovascular toxicity, as well as resistance to heat. It is challenging to monitor the temperature during the treatment since the temperature may change in vivo due to tissue specifity and thermo-regulatory mechanisms of the body. The difficulty of temperature monitoring complicates the controlling on the exact thermal dose and the toxicity. There are studies focusing on precisely positioning heat-delivery devices by ultrasound [2]. For instance, a research claimed the low power cumulative high-intensity focused ultrasound (HIFU) shows significant benefit in pain control and the survival rate with fewer side effect compared with traditional HIFU treatment, which is suitable for stage IV pancreatic cancer patients [8].

Hyperthermia influences the proliferation activity of tumor cells which are thermosensitive at the M and S phases in mitotic cycle. It is especially cytotoxic to oxygenated and hypoxic cells equally sensitizing both to radiation. Most of the tumor cells are in hypoxic or prenecrotic area where blood vessels lack. The

sparsely ionizing radion kills well-oxygenated tumors effectively but has trouble on hypoxic area. Under hypoxic condition, hyperthermia could inactivate tumor cells and improve the oxygenation of both chronic and acute hypoxic cells. Hyperthermia also reduces immune suppression and immune escape of cancer and inhibits their resistance to radiotherapy and chemotherapy [9]. Besides, it also helps the absorption of anticancer drug in cancer cells.

Cancer immunotherapy aims at improving the natural ability of immune system against tumor. It is receiving more and more attention in recent years. Tumor cells produce tumor specific antigens (TSA) which are tumor markers and can be targeted by immune system. Immunotherapy includes active immunotherapy and passive immunotherapy.

The active immunotherapy stimulates host's immune system to induce expelling responses to tumors specifically. Dendric cells are antigen-presenting cells (APCs) that could induce anti-tumor response by presenting antigens to lymphocytes. The approved drug for prostate cancer, sipuleucel-T, recognizes prostatic acid phosphatase from APCs [10]. The cell-mediated therapy extracts patient's immune cells, such as natural killer (NK) cells, lymphokine-activated killer cells, cytotoxic T cells and dendritic cells, genetically enables the cells to recognize TSA after returning into the body. In CAR-T cell therapy, chimeric antigen receptor is engineered onto T cells to target tumor cells more specifically [11, 12], such as Tisagenlecleucel to treat acute lymphoblastic leukemia and Axicabtagene ciloleucel for diffuse large B-cell lymphoma.

The passive immunotherapy promotes the ability of immune system to attack tumors, which includes immune checkpoint inhibitors and cytokines. Immune checkpoint inhibitors set T cells active to destroy cancer cells by blocking immune checkpoint proteins on T cells from binding with the partner proteins on cancer cells, such as inhibitors of PD-1, PD-L1 or CTLA-4. Cytokines are proteins mediating cell-cell communication [13]. Some cytokines could enhance immune effects against cancer. Interferon-alpha and interleukin-2 were approved by FDA in US to treat some malignancies.

Not like radiation therapy, hyperthermia could be applied repeatedly for its minor damage on normal tissues, which makes hyperthermia an combinable method of immunotherapy, should it benefit the treatment. Hyperthermia activates immune cells including cytotoxic T lymphocytes (CTLs), dendritic cells (DCs), and natural killer (NK) cells, thus inhibits immune suppression in cancer. The expression of ICAM1 and CCL21 in high endothelial venules (HEVs) increases during hyperthermia inducing the adhesion and migration of DCs and T-cells toward HEVs. The secretion of IFN(interferon)-gamma and IL-2 from T-cells increases significantly after whole-body hyperthermia, which could be explained by the enhanced fluidity of cell membrane triggered by heat that accelerates the crosstalk of T-cells with antigen-presenting cells. The whole-body hyperthermia increases the synthesis of heat-shock proteins (HSPs) which affects the T-cell function and acts as molecular chaperones.

Hyperthermia induces HSPs releasing and increases DC priming against tumor antigen. However HSP in hyperthermia also shows some adverse functions. HSPs also mediate thermotolerance which might help tumor survival and result in the generation of thermotolerant tumor. Hsp70 is an apoptosis inhibitor preventing aggregation, remodeling folding pathways, and regulating activity of cancer cells in hyperthermia.

The nonspecific anticancer immune reactions could be strengthened by hyperthermia. As an effective anticancer factor, NK cells target those cells lack of MHC class I molecules which is the result of cancer immune escape. The hyperthermia reinforces the clustering ability of NK cell-activating receptors and the expression of NK cell-activating ligands. DCs could recognize the cancer antigen made by NK cells and cancer interaction for triggering T-cells based immune response. The regulatory T cells (Tregs) will be generated during cancer treatment by the regulation of immune system and immunological tolerance system. Animal models proved the efficacy of immunotherapy improvement after eliminated Tregs. Hyperthermia could enhance the cytotoxicity of NK cells to against Tregs as well.

So far hyperthermia therapy is not yet widely used in clinical, much less than radiation therapy. The major limitations may be the real-time accurate mornitoring in tissue and establishes of HT into clinical treatment workflows. With new technologies under development improving precisive HT operation, more attention from oncologists is necessary to explore the benefit of HT in cancer treatment.

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