Cancer Treatments Combined with Thermal Therapy

Subjects: Engineering, Biomedical

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As a safe and minimal-invasive modality, thermal therapy has become an effective treatment in cancer treatment. Other than killing the tumor cells or destroying the tumor entirely, the thermal modality results in profound molecular, cellular and biological effects on both the targeted tissue, surrounding environments, and even the whole body, which has triggered the combination of the thermal therapy with other traditional therapies as chemotherapy and radiation therapy or new therapies like immunotherapy, gene therapy and so on. The combined treatments have shown encouraging therapeutic effects both in research and clinic. The heating of tissue can be realized by either electromagnetic or mechanical waves. Typical treatments include radiofrequency ablation (RFA), microwave ablation (MWA), laser interstitial thermal therapy (LITT), magnetic particle hyperthermia (MPH), photothermal therapy (PTT), and high intensity-focused ultrasound (HIFU). Thermal ablation uses a temperature higher than 55 °C to induce direct coagulative necrosis of the targeted tumor tissue. In these ablation treatments, due to the thermal diffusion, the region of the tissue that surrounds the region with high lethal temperature will experience temperature that is in the range of hyperthermia. Cryoablation is usually realized by high-pressure gas or low-temperature liquids. Clinical thermal therapy techniques have been reported to show promising results from either in vitro studies or clinical retrospective evaluations in combination with other tumor treatment modalities, which include chemotherapy, radiation therapy, immunotherapy, and other minimally invasive therapy.

Keywords: cancer ; thermal therapy ; combination ; physical therapy

1. Chemotherapy Combined with Thermal Therapy

Chemotherapy is a major cancer treatment. Chemotherapeutic agents such as brivanib, doxorubicin (DOX), erlotinib, everolimus, lenvatinib, linifanib, ramucirumab, regorafenib, sorafenib, sunitinib, tivantinib [1] are delivered by oral protocol, bolus injection, and continuous infusion to circulate in the whole body [2]. These agents inhibit the kinases and key factors related to cell proliferation and thus kill the cancer cells. Local thermal treatments have already been shown to be able to increase chemotherapy outcomes in clinical applications, but the enhancement varies with different kinds of cancers. In lung cancer (ICC), the medium survival (95% CI)-OS of ablation-chemotherapy (RFA/MWA as thermal therapy) almost doubled compared to that in the chemotherapy- only group after propensity score matching (PSM) [3]. When combined with chemotherapy in lung cancer, MWA/RFA increases median PFS time up to 10.4/9.2 months [4] respectively. In ovarian cancer liver metastasis (OCLM), the 1-, 2-, and 3-year OS rates of RFA plus chemotherapy were 93.3%, 80.0%, and 53.3% respectively, compared to 79.5%, 60.1%, and 42.1% in the chemotherapy alone [5].

The performance of thermally enhanced chemotherapy can be summarized as increased DNA damage and chemotherapeutic drug targeting, inhibition of DNA repair, formation of an acidic environment, and increased sensitivity to chemotherapeutic agents especially for cells in the S phase [6][7][8]. Dou, J. et al. [9] found that the elevated intracellular Ca^{2+} caused by combining MWA and DOX destroyed the homeostasis of tumor cells and decreased the mitochondrial inner membrane potential, resulting in massive apoptosis in vitro studies on HepG2 cells and in vivo studies on mice.

When combined, the dosage thresholds of either chemotherapeutic agents or thermal energy either hyperthermia or thermal ablation can be reduced. In treating DU145 prostate cancer cells, the combination of HIFU and Sorafenib decreases the thresholds by almost 67% and above 80% respectively compared to HIFU alone and Sorafenib alone according to cell viability [10].

Increase in cryotherapy efficiency has also been observed when used with chemotherapy [11][12]. Application of cisplatin increased lethal cooling temperature for bladder cancer from −25 °C to −15 °C [11]. With 30 min of 1 μM cisplatin exposure before cooling to −15 °C, the killing effect based on the survival rate of SCaBER cells was increased 4.6 times compared to the group with freezing alone. The low dosage of the chemotherapeutic agents used is not enough to kill the cells directly but is believed to have prevented the initiation of cellular repair mechanisms necessary for surviva1 [11], substantially activating caspase-3 within the nucleus to induce apoptosis [12] or increase the Bcl-2 to Bax ratio leading to a pro-death tendency [13], thus increases the low-temperature induced damage.

When the chemotherapeutic agents are packed as nano-drugs, the spatial distribution can be further controlled and targeted to decrease the byproduct of chemotherapy by application of thermal energy [14] with therapeutic effect enhanced and side effects decreased from the followed aspects.

(1) Local heating is used to break the structure of the nano-particles and release the chemotherapeutic agents [15][16][17][18]. Only after being heated to a certain temperature, the temperature-sensitive liposomes will release the chemotherapeutic agents [10]. A newly designed microneedle consisting of photothermal agents and DOX is used to realize a NIR-II light-triggered heating, local drug release, and NIR-II fluorescence imaging at the same time [19]. Furthermore, through a programmable and wireless control of heating duration, the amount of DOX released from the temperature-sensitive liposomes is successfully controlled [20]. Temperature sensitive nano-particles can also be made from different materials such as Evans blue derivative-functionalized gold nanorods [21], $CoFe_2O_4$@PDA@ZIF-8 sandwich nanocomposite [22], DNA-templated silver nanoclusters and polydopamine nanoparticles [23], camptothecin-conjugated gold nanorods [24], and ZIF-8 coated ZrO_2 [25] for thermally controlled release of the drug. These particles are also found to be able to increase local adsorption of heat at the same time. And for PTT chemotherapeutic-drug loaded with photothermal transduction agents (PTAs) have shown higher photothermal conversion efficiency and increased penetration of PTT. Combining the functional effects of PTT-mediated thermal effects, such as controlled drug release and enhanced chemical response of targeted tissues, synergistic strategies can achieve a cure of larger tumors as well as lesions with distant metastatic and disseminated.

(2) Heating enhances vascular permeability, increases oxygenation, decreases interstitial fluid pressure, reestablishes normal physiological pH conditions, thus increases extravasation of the nano-drugs from the bloodstream and cellular uptake of the chemotherapeutic agents, and, finally, enhances the killing effect [26][27].

(3) Targeting of the thermal therapy to the tumor is improved by the nano-drugs designed [23][28]. When nano-drugs in the cancer tissue serve as multiple thermal sources, the special distribution of the nano-drugs generates a unique heating pattern and thus helps further focus the application of thermal energy [29]. Besides, by surface modification, the nano-particles would target the cell surface [14][30] or even subcellular structures such as mitochondria [31] and thus realizing heating targeted region accordingly. Also. by using materials with different thermal, conductivities, the temperature distribution inside the tissue may be changed accordingly to the increased thermal energy accumulation in the targeted tissue.

2. Radiation Therapy Combined with Thermal Therapy

Radiation therapy uses high-energy photon radiation such as X-rays, and gamma (γ)-rays to generate ROS and induce single-strand breaks (SSB) and double-strand breaks (DSB) in DNA to terminate cell division and proliferation [32]. The combination of thermal therapy and radiation therapy can date back to 1975 [33]. Heating to 45 °C several minutes before/during radiation effectively radio-sensitized the radio-resistant G1/S phase cells. Thermally enhanced radiation therapy has also been found to alleviate the hypoxia degree of tumor and a decrease in the expression of DNA repair-related proteins [34].

Improved local control in spinal metastases has been found by combined thermal ablation of hyperthermia and radiation compared to hyperthermia alone [35]. With the development of non-invasive hyperthermia in 2018, where a 12 antenna applicator for targeted selective heating [36] was designed, the heating was focused into the tissue deep-seated in the body for advanced head and neck carcinoma 1–3 h after irradiation. The maximum temperature and median temperature can reach 42.3 °C and 39 °C respectively. The response rates after 3 months were 46% (complete) and 7% (partial) and no severe complications or thermal toxicities were observed. It was provided the possibility for synchronous heating and radiation though the procedure of combined therapy was made by alternating heating and radiation. Photothermal therapy (PTT) is another hyperthermia modality used before or after radiation therapy [37][38][39]. Other than the heating effects, the metal ions of the photosensitizer strongly absorb, scatter, and re-emit radiation energy, and thus generating extra singlet oxygen to amplify the local radiation dose [40].

Thermal ablation is also used together with radiation. With developed in vivo pancreas models in swine, the scores of the injury to target in radiation therapy applied within 12 h followed HIFU group was found to be almost 2–3 times of the HIFU only group and about 1.5 times to the radiation therapy only group [41]. Large areas with reactive/swollen cells were observed by H&E staining. Radiation would help ensure the complete killing of the cells located at the outer ring of the carcinoma which is sensitive to radiotherapy but may escape from the thermal energy due to large cooling from blood perfusion in this region.

In these cases, thermal therapy and radiation therapy are still applied using separate machines. The time duration between the joint treatments sometimes is quite long, where the synergistic effect of both treatments found through in vitro experiments hardly exists in these clinical trials. The integration of synchronous thermal ablation/hyperthermia with radiation therapy needs further study to realize a better design of the treatment sequences and even better treatment outcomes than current findings.

3. Immunotherapy Combined with Thermal Therapy

3.1. Immune Checkpoint Blockade Therapy Combined with Thermal Therapy

Immune checkpoint inhibitors (ICIs) such as programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) antibodies and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibodies have been approved by the FDA for treatment of malignant melanoma, lung cancer, and lymphoma [42]. The immune checkpoint activity is inhibited to counteract the suppressive effect of the tumor microenvironment on the host's immune activity, and thus reactivating the T-cell-based antitumor immune response. Therefore, an adequate and effective immune response is critical for successful oncology treatment. However, insufficient tumor antigenicity, lack of lymphocytes, and immunosuppressive tumor microenvironment often obstruct this therapy [42]. The immune-related adverse events (irAEs) [43] have been also widely observed clinically, including cardiotoxicity [44][45], pancreatic injury [46], thyroid Dysfunction [47], and infectious complications [48][49].

Thermal therapy itself has been reported to result in certain anti-tumor immune effects but not strong enough for metastases treatment [50][51]. A combination of thermal therapy and immunotherapy [52][53] has been studied to realize a positive immune response. The medium recurrence-free survival (RFS) increased from 19.3 weeks to 39.1 weeks when the PD-1/PD-L1 antibodies were added to RFA, while the OS increased slightly from 47.6 weeks to 51.0 weeks in a retrospective study of 127 patients with HCC [54]. In renal cell carcinoma (RCC) [55] and colorectal carcinoma [56], the combination of RFA/MWA and immune checkpoint inhibitors (ICIs) also showed potential in complete local control, prevention of the growth of metastases, and significant increase of the patient's survival rate.

These results are very promising and many studies have looked into the mechanisms underlying the joint treatment. RFA and MWA have been proven to serve as antigen sources for immunotherapy in B16-OVA tumor-bearing mice [57]. The induction of heat shock proteins, acute phase response, and mobilization of antigen-presenting cells and effector lymphocytes after local thermal ablation may have enhanced the immune response from the ICI treatment [58]. Similarly, a couple of studies have been proposed to combine HIFU with immunotherapy. The advantages of such combination can be concluded as: (1) Thermal therapy induced increase of IFN-γ, HSP 27, HSP 70 concentrations and decrease of IL-10, IL-4, TGFb-1, and TGFb-2 concentrations to help improve the antigen-presenting capability [59][60][61]; (2) Combined treatments also resulted in increased concentrations of dendritic cells and decreased concentrations of IL-10 and CD4+Foxp3+, leading to more efficient priming and activation of T-cells [62][63]; (3) Combined therapy induced elevated long-term memory markers CD4+CD44+hiCD62+low and CD8α+CD44+hiCD62+low

for prevention of tumor recurrence and thus enhanced sensitization of ICIs therapy [64]. In addition, the mechanical effect of HIFU also plays a significant part in improving the anti-tumor immune response, as the addition of the microbubbles was found to have induced the Th1 reaction to strengthen the activity of DC and cytotoxic lymphocytes [65].

3.2. CAR-T Therapy Combined with Thermal Therapy

CAR-T cell therapy (Chimeric Antigen Receptor T-Cell) is a T cell-based therapy, which combines the technologies of immunotherapy and gene therapy [66]. It first introduces a gene to the person's T cells to modify the immune cells to attack cancer cells. In recent years, CAR-T cell therapy combining thermal therapy is receiving a lot of attention from researchers. Local thermal therapy is able to modulate the expression of the heat shock promoter through temperature control [67][68], allowing induction of the associated transgene only in heated areas.

Because of its precise and rapid heating properties, focused ultrasound(FUS) has a great application for the control of transgene expression in oncotherapy. Wu, Yiqian et al. [67] have achieved specific activation and direct control of CAR-T cells without any exogenous cofactor, suppressing tumor growth apparently in vivo. The heat-shock-protein promoter they used can sensitively control the expression state of chimeric antigen receptor(CAR) under the simulation of FUS, avoiding the problem of off-target tumor toxicity associated with CAR-T cell therapy. In addition, Miller, Ian C et al. [68] achieved the enhanced intratumoral activity of CAR-T cells under photothermal control. In vitro experiments showed that transgene had over 60-fold-higher expression without any influence on normal physiological activities under mild temperature elevations(to 40–42 °C) for 15–30 min. While in vivo study found that photothermal conversion of gold nanorods

stimulated heat-shock elements(HSEs) and core promoters to dive IL-15 superagonist activation, greatly enhancing the anti-tumor capacity of CAR-T therapy.

3.3. Other Immunotherapies Combined with Thermal Therapy

Compared to thermal ablation techniques, it is believed that cryoablation preserves more intact tumor antigenic structures to trigger a tumor-specific protective immune response [50][69]. Shao qi et al. have demonstrated that cryoablation (−80 °C, 30 min) on B16 cancer cells resulted in an 8.25 times release of natural proteins and activated a stronger T-cell immune response, which is 1.6 times more than the heating treatment group (50 °C, 30 min) [70]. Combining cryoablation, IFN-γ and VEGF signaling pathways are activated and further enhanced, providing a good induction pathway for immune cell infiltration in the tumor microenvironment [71]. In addition to the ability to increase the killing activity of immune cells such as T cells and NK cells, the underlying mechanism may contribute to the modulation of immune responses by promoting a release of Hsp70 and reducing Ki67 activity [72][73][74]. Recently, Campbell, M.T. et al. conducted a preliminary study using Tremelimumab immunotherapy with and without cryoablation in 29 patients with metastatic renal cell carcinoma [71]. They found a significant increase in T-cell infiltration in the tumor microenvironment of patients after cryo-trimethoprim combination therapy and laid an important foundation for subsequent combination therapy for patients with mccRCC. Except for the usage of ICIs and CAR-T therapy, some other immunotherapies such as the usage of toll-like receptor (TLR) agonists, adoptive cell therapies (ACTs), and uptake of epigenetic modulators can also be combined with cryoablation to enhance its immunogenicity, and thus stimulate the immune system and lead to good synergistic immune-mediating effects [75][76][77][78].

4. Gene Therapy Combined with Thermal Therapy

Even since the concept of gene therapy was first put forward by Friedmann in 1972 [79], it has become an important modality for cancer therapy. This technology can treat cancer at its genetic root by editing a gene to enhance the efficacy of target cells, significantly improving the survival rate of cancer patients [80]. However, the major problem of this therapy is the accurate delivery of the gene expression vectors and the effective expression of target genes without affecting the cells' normal regulatory activities [81]. As common gene therapy vectors, Adenovirus, lentivirus, and adeno-associated viruses (AAVs) gene therapy vectors have potential immunostimulatory effects, lower targeting and oncogenic effects [82][83][84]. Non-viral delivery vehicles such as liposomes, nanoparticles, polymers, and dendrimers have low transfer efficiency, and most of the transduced genes in this therapy are metabolized and eliminated by the liver and kidneys [85][86].

In earlier studies, researchers have demonstrated that heating can rupture tissue, and improve cell metabolism & cell membrane permeability, thereby increasing the efficiency of gene transfer [87][88].

Results of these studies have shown that through precise control of the thermal parameters, control of genetic engineering for therapeutics can be achieved [67]. The combining of thermal and gene therapy for cancer treatment will help lay an important foundation for the development of safer and more controllable application of gene therapy in clinics [89].

5. Other Minimally Invasive Therapy Combined with Thermal Therapy

Other than the above therapies that can be greatly enhanced by thermal therapy, some other local minimally invasive treatments such as TACE [90], TARE [91][92], and IRE [93][94] have also been used together with the thermal therapies. RFA has been shown to increase the OS and progression-free survival (PFS) of unresectable pancreatic cancer [95], HCC [96][97][98] and ICC [99] treated with TACE. Disruption of the angiogenesis and blood supply of the tumor enhanced the therapeutic outcome of TACE [90]. The combination of cryoablation and TACE has resulted in a much-reduced blood supply to the tumor than any single modality. Similarly, transarterial radioembolization (TARE) has shown a highly increased radiation effect when in combination with thermal therapy. By lowering the lethal electric field threshold for Irreversible Electroporation(IRE) [93][94] by heating from RFA, the therapeutic outcome of IRE was obviously increased.

Abbreviations

CAR-T	**Chimeric Antigen Receptor T-Cell**
CTLA-4	**cytotoxic T-lymphocyte-associated protein 4**
DOX	**Doxorubicin**

HIFU	**High intensity focused ultrasound**
HSPs	**Heat shock proteins**
ICIs	**Immune checkpoint inhibitors**
LITT	**Laser interstitial thermal therapy**
MPH	**magnetic particle hyperthermia**
MWA	**Microwave ablation**
OS	**Overall survival**
PD-1	**Programmed cell death protein 1**
PD-L1	**Programmed death-ligand 1**
PTT	**Photothermal therapy**
RFA	**Radiofrequency ablation**
TACE	**Transcatheter arterial chemoembolization**
TAMs	**Tumor-associated macrophages**
TARE	**Transarterial radioembolization**

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