



ORIGINAL ARTICLE / *Research and new developments*

Enhanced antitumor efficacy through microwave ablation in combination with immune checkpoints blockade in breast cancer: A pre-clinical study in a murine model

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KEYWORDS

Microwave ablation;
Immune checkpoints blockade;
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T-cell

Abstract

Purpose: The purpose of this study was to investigate the therapeutic efficacy of the combination of microwave ablation (MWA) in combination with immune checkpoints blockade in the treatment of breast cancer using the 4T1 tumor-bearing mice model.

Materials and methods: We treated tumor-bearing mice with MWA, programmed cell death protein1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) blockade (P+C), MWA plus PD-1 and CTLA-4 blockade (combination therapy), or no-treatment. Survival time was evaluated with the Kaplan-Meier method comparing survival curves by log-rank test. On day 15 after MWA, five mice from the combination therapy group received tumor rechallenge with 4T1 or CT26 cells and the volumes of rechallenge tumor were calculated every 5 days. Immune cells were identified by immunohistochemistry and flow cytometry, and the concentrations of plasma interferon- γ (IFN- γ) were identified by enzyme-linked immunosorbent assay (ELISA).

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Results: The combination therapy significantly prolonged tumor-bearing mice survival compared to no-treatment group, P+C group or MWA group ($P < 0.001$, $P < 0.001$ and $P = 0.01$, respectively) and protected most surviving mice from 4T1 tumor rechallenge ($P = 0.002$) but not CT26 tumor rechallenge ($P = 0.905$). Both local and systemic CD8⁺ T-cell responses were induced by MWA (all $P < 0.05$) and further augmented by subsequent administration of PD-1 and CTLA-4 blockade (all $P < 0.05$). Plasma IFN- γ concentrations were significantly elevated in the combination therapy group compared to no-treatment group, P+C group or MWA group ($P < 0.001$, $P < 0.001$ and $P = 0.01$, respectively).

Conclusion: MWA combined with immune checkpoints blockade could synergistically enhance antitumor efficacy with augmented specific immune responses, and the combination therapy is a promising approach to treat breast cancer.

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Introduction

In situ tumor ablation, such as radiofrequency ablation (RFA), laser ablation or microwave ablation (MWA), has received increasing attention in the last decades [1–3]. As minimally invasive therapies for focal cancer, these thermal ablations have obtained encouraging results. MWA is a relatively new ablation technique that generates electromagnetic heating and causes focal hyperthermic injury to destroy tumor tissues [4], which has been proven to be an effective and safe treatment for liver, lung, kidney and breast tumors [5,6]. In addition to directly destroy tumor tissues, MWA can lead to the release of large amounts of cellular debris in situ, which can serve as a source of tumor antigens to elicit hosting adaptive immune responses against tumors [7]. However, MWA-induced immune responses are weak and not sufficient to prevent tumor recurrence [8]. Thus, additional immunomodulatory strategies are needed to enhance the antitumor immunity, and Li et al. identified that combining MWA with immunotherapy had demonstrated a synergistic effect on tumor rejection with augmented immune responses [9].

Immune checkpoints are a series of inhibitory pathways that are crucial for modulating the intensity and duration of immune responses, and antibodies that block immune checkpoints have shown to enhance antitumor immune responses [10]. As the first immune checkpoint inhibitor for clinical testing in cancer therapy, Ipilimumab, an anti-CTLA-4 antibody, improved overall survival with a favorable safety in two randomized controlled phase III trials of unresectable advanced melanoma [11–13], so it became the first immune checkpoint inhibitor approved for advanced melanoma by the US Food and Drug Administration (FDA) in 2011. In addition, PD1/PD-L1/-L2 pathway inhibitors also gained tremendous progress, and so far there were some agents targeting PD-1 approved by FDA for metastatic melanoma, non-small cell lung cancer, renal cell carcinoma, treatment-refractory unresectable colorectal cancer and head and neck squamous cell carcinoma [14–16]. Though immune checkpoints inhibitors had made great progress, there were

still a small subset of cancer patients achieving durable clinical responses to immunotherapy [17], which necessitated the development of combinatorial regimens with immunotherapy to make immune checkpoints inhibitors benefit to more cancer patients. Thus, many clinical trials are currently investigating the efficacy of immune checkpoints blockade in variety of solid tumors in combination with other modalities such as, other immunomodulatory agents, cancer vaccines, chemotherapy, or radiation [18,19]. Hodi et al. found that the combination immunotherapy of anti-PD-1 and anti-CTLA-4 was more effective than any alone administration of the two antibodies in both animal models and patients [20]. Rebecca et al. identified that combining tumor cryoablation with anti-CTLA-4 had augmented anti-tumor immunity and rejection of tumor metastases in a tumor-bearing mice model [21], and Heather et al. further testified that the combination of cryoablation and ipilimumab enhanced synergistically anti-tumor immunity in women with breast cancer [22]. Though MWA is technically feasible for the treatment of breast cancer, there is still room to improve the efficacy of MWA in the treatment of breast cancer.

The purpose of this study was to investigate the therapeutic efficacy of MWA in combination with immune checkpoints blockade in the treatment of breast cancer using the 4T1 tumor-bearing mice model.

Material and methods

Cell line

Murine breast cancer cell line 4T1 and murine colorectal adenocarcinoma cell line CT26 were obtained from Chinese Academy of Sciences (Shanghai, China). Cells were maintained in RPMI 1640 supplemented with 10% fetal bovine serum, 100 $\mu\text{g/ml}$ streptomycin, and 100 unit/ml penicillin at 37 °C in humidified atmosphere containing 5% CO₂. All cell culture reagents were purchased from Invitrogen (Shanghai, China).

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