Laser immunotherapy for treatment of patients with advanced breast cancer and melanoma

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Abstract  Laser immunotherapy (LIT) was developed for the treatment of metastatic tumors. It combines local selective photothermal interaction and active immunological stimulation to induce a long-term, systemic anti-tumor immunity. During the past sixteen years, LIT has been advanced from bench-top to bedside, with promising outcomes. In our pre-clinical and preliminary clinical studies, LIT has demonstrated the capability in inducing immunological responses, which not only can eradicate the treated primary tumors, but also can eliminate untreated metastases at distant sites. Specifically, LIT has been used to treat advanced melanoma and breast cancer patients during the past five years. LIT was shown to be effective in controlling both primary tumors and distant metastases in late-stage patients, who have failed conventional therapies such as surgery, chemotherapy, radiation, and other more advanced approaches. The methodology and the development of LIT are presented in this paper. The patients’ responses to LIT are also reported in this paper. The preliminary results obtained in these studies indicated that LIT could be an effective modality for the treatment of patients with late-stage, metastatic cancers, who are facing severely limited options.

Keywords: Laser immunotherapy, imiquimod, glycated chitosan, photothermal effect, systemic immune responses, metastasis, melanoma, breast cancer.

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1. Introduction

Laser immunotherapy (LIT) is a new approach for cancer treatment using host immune system to fight the disease. LIT was proposed in 1997, which provides a convenient, efficient means to directly destroy the tumors at the treatment site and to induce tumor-specific host immune responses. LIT utilizes a near-infrared laser, a light-absorbing agent, and an immunoadjuvant for the selective photothermal interaction and the targeted immunological stimulation. Our pre-clinical studies and preliminary clinical trials using LIT for the treatment for late-stage melanoma patients have shown promising outcomes.

Photothermal interaction using a near-infrared laser and a light-absorbing agent can induce a high temperature increase in the target tissue, which creates a selective tissue destruction zone covering the target tumor mass. Although this thermal reaction usually does not result in complete destruction or total acute eradication of target tumors, it causes tumor cells swell and break into pieces, allowing the release of antigens with the increase of temperature. These antigens include tumor-associated antigens, thermally induced heat shock proteins (HSPs), and a large number of self-antigens. Antigen presenting cells (APCs), particularly dendritic cells (DCs), can capture these antigens and migrate to lymph nodes. They present the antigens to T cells to induce an immune response that can be effective against specific tumor cells. The LIT-treated tumors in patients serve as the sources of cancer antigens in situ and all the cancer antigens come from the patients’ own tumor cells, as in the case of autologous vaccination. In addition, without in vitro procedure for pre-selection for specific cancer antigens, the whole cell serves as the vaccine in LIT.

The immune systems of late-stage cancer patients are often severely compromised and unable to respond vigorously to the traditional vaccination. Therefore, two different immunoadjuvants, imiquimod and glycated chitosan, were applied to further enhance the immune response induced by the photothermal effect. Imiquimod, a special immunological modulator, activates immune cells through a toll-like receptor (TLR7), which are commonly involved in pathogen recognition. Imiquimod can also induce localization and activation of Langerhans cells in treated skin, allowing them to subsequently migrate to local lymph nodes to activate the adaptive immune system. Natural killer cells, macrophages, and B-lymphocytes are also activated by imiquimod. Glycated chitosan (GC) is a newly invented immunoadjuvant. According to our ongoing study (unpublished data), GC can directly activate DCs, and enhance antigen presentation to DCs, causing proliferation of T cells. The combined thermal treatment and GC stimulation can achieve even higher levels of T cell proliferation.

The present study is designed to investigate the clinical effects of LIT in the treatment of patients with late-stage melanoma and breast cancer.

2. Materials and Methods

2.1. Lasers

An 805-nm diode laser (AngioDynamics, Queensbury, NY) was used for the melanoma study. The light was delivered to the melanoma treatment surface through an optical fiber with a micro-diffusion lens. For the breast cancer study, an 805-nm laser (ImmunoPhotonics, Inc., Columbia, MO) was used and the laser light was delivered by an optical fiber to the breast cancer surface with a specially designed hand-piece (Figure 1). The laser power density at the surface of the skin was 1 W/cm² for both studies.

2.2. Indocyanine green (ICG)

ICG, obtained from Arkon Inc. (Buffalo Grove, IL), is a kind of cyanine dye used in medical diagnostics, which has a peak spectral absorption at about 800 nm. ICG can strongly absorb the light
energy of the 805-nm laser. The interaction between ICG and 805-nm laser can induce the photothermal effect, which can increase the temperature in the tissue of treatment area. A solution of 0.25% ICG was injected at a dose of 0.5 mL/cm³ prior to laser irradiation.

![The 805-nm laser and the optical fiber with the hand-piece from by ImmunoPhotonics, Inc.](image)

**Figure 1.** The 805-nm laser and the optical fiber with the hand-piece from by ImmunoPhotonics, Inc.

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2.3. Imiquimod

Imiquimod (Aldara™) was purchased from 3M Pharmaceuticals (St. Paul, Minnesota, 5% cream under plastic occlusion). For melanoma patients, imiquimod was applied twice daily for two weeks before laser irradiation.

2.4. Glycated chitosan (GC)

GC was developed by our research group\(^2\). GC of 1% concentration was used for the treatment of breast cancer patients. GC was injected around the tumor for immunological stimulation immediately after laser irradiation.

2.5. Laser immunotherapy

For melanoma treatment, a 6-week cycle of LIT was carried out for each designated 200-cm² treatment area with the following five steps. (1) Topical application of imiquimod for 2 weeks; (2) Asepsis followed by local administration of anesthetic (lidocaine 2% with adrenaline); (3) Local injection of ICG; (4) Two times of laser irradiation, the first one was applied at the beginning of week 2, and the second one at the beginning of week 4; (5) Two weeks of imiquimod application after second laser session.
For breast cancer treatment, a 4-week cycle of LIT was carried out with the following steps: (1) Asepsis followed by local administration of anesthetic; (2) Local injection of ICG; (3) Laser irradiation; and (4) Local injection of GC.

2.6. Assessment of clinical outcomes

Toxicity was assessed according to National Cancer Institute Common Toxicity Criteria, version 3.0. The primary efficacy parameter was the best overall response by investigator’s assessment using the Response Evaluation Criteria in Solid Tumors (RECIST).

3. Results

3.1. Patients

Eleven patients were enrolled in the melanoma study using laser immunotherapy with imiquimod from 2004 to 2010. Ten patients were enrolled in our breast cancer study using laser immunotherapy with glycated chitosan since September 2009. All the patients were more than 18 years old and had histologically confirmed stage III or IV melanoma or breast cancer according to the criteria of modified American Joint Commission on Cancer (AJCC) staging system. All the patients are not available for traditional modalities.

3.2. Safety

LIT was generally well tolerated. Only local irritation was seen in all the patients treated by LIT. The most frequently reported adverse events were rash, pruritus, pain and edema. These side effects are induced mainly by the photothermal effects of LIT. The most severe side effects generally occurred during the first treatment cycle. The severity of these side effects was correlated with the previous irradiation therapy history of the treatment area. No grade 4 AEs were noted in our trials.

3.3. Efficacy

All the lesions at the treatment sites of the enrolled patients responded to LIT. In melanoma patients treated by LIT, complete response (CR) and partial response (PR) were observed in 5 patients. The objective response rate was 45.5%. One patient achieved stable disease (SD) and one patient had progression disease (PD).

In breast cancer patients treated by LIT, CR was observed in 1 patient, PR in 6 patients, SD in 2 patient and PD in 1 patient. The objective response rate was 70.0%, and the clinical beneficial response rate was 90.0%. All the patients with advanced breast cancer are still alive at the time of this report.

Figures 2 and 3 show the volume changes of the primary lesions and lung, liver and brain metastases for two stage-IV breast cancer patients. The data presented in Figure 2 is for a 40-year old patient. Before LIT, the diameter of primary lesion on the left breast was 4.0 cm. It completely disappeared after two LIT treatments. This patient had three liver metastatic nodules with diameters of 6.0 cm, 2.5 cm, and 2.0 cm, respectively, before LIT treatment. Five months after LIT treatment, two liver nodules were stable, and one metastasis disappeared (Figure 2).

The data presented in Figure 3 are for an 85-year old patient, who was diagnosed with stage IV triple-negative breast cancer, whose breast tumor does not express the genes for estrogen receptor (ER), progesterone receptor (PR), or Her2/neu. This subtype of breast cancer is clinically characterized as more aggressive and less responsive to standard treatments and with extremely poor overall prognosis. This
patient had a 3.8-cm tumor in the right breast and a 3.6-cm tumor in the left breast before LIT treatment. Furthermore, this patient also developed metastases in the lungs and the brain. During the course of nine months, this patient received five LIT treatments. Her tumor in the right breast regressed completely while only a very small residual tumor was seen on the left breast (Figure 3). Brain metastasis with a diameter of 0.9 cm disappeared eight months after LIT treatment. The diameter of metastasis in the left lung decreased from 5 cm to 3.2 cm.

4. Conclusion

As a newly invented technology, LIT faces many challenges and many questions need to be further investigated. This report presented the preliminary clinical outcomes of LIT. Eleven advanced melanoma patients and ten advanced breast cancer patients were enrolled in our clinical trials. Each patient received at least one cycle of LIT treatment. The side effect is very limited, and it is well tolerated. After LIT treatment, not only the primary tumors responded well in the majority of the patients, the metastases at distant sites, such as the lungs, liver, and brain, were also responded positively in most stage IV patients. The metastases in most cases were either reduced in size or became stable. Our results show that LIT is not only a useful palliative modality for local primary tumors, but also a powerful method to
control distant metastases. With further understanding of its fundamental mechanisms and continued research, it is believed that LIT will become a mature and necessary method for late-stage cancer treatment.

Acknowledgements

This research is supported by US National Institutes of Health (P20 RR016478 from the INBRE Program of the National Center for Research Resources) and National Natural Science Foundation of China (No. 81000994).

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