Anti-tumor effects and immunological response following immune stimulating interstitial laser thermotherapy

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Introduction

Local tumor destruction can be achieved by many means including laser thermotherapy, radiation, radiofrequency ablation and other techniques. Immunostimulating interstitial laser thermotherapy (imILT) was developed to create effective local ablation as well as optimizing subsequent immunologically mediated anti-cancer effects following the tissue destruction. imILT is a suitable method for all solid tumors and have successfully been used clinically to treat tumors situated in breast, liver, pancreas, lymph nodes and subcutaneously. Local control using the method is possible if radical treatments are performed and reported adverse events related to the treatment have all been manageable [1-3]. Long-term follow up of a group of breast cancer patients treated with imILT showed no long-term adverse effects [4].

1.

Method and instrument

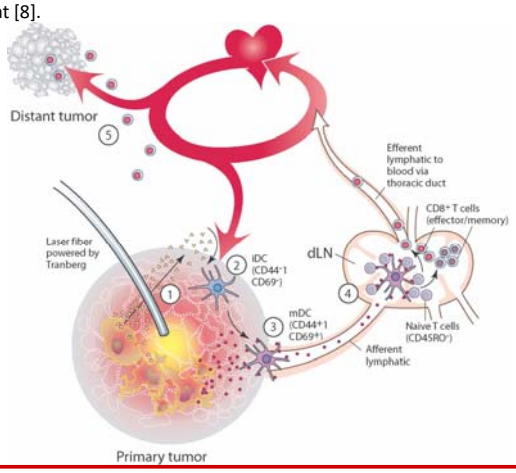
imILT treatment is performed using the TRANBERG Thermal Therapy System. It consists of a laser unit delivering laser light of 1064 nm trough a glass fiber and a temperature probe feeding temperature data back to the laser unit. The laser fiber is inserted into the targeted tumor tissue and the temperature probe is placed in the perimeter of the ablation zone. Heat is generated when light emitted from the fiber is absorbed in the tissue and light output from the laser unit is regulated based on temperature information from the temperature probe to keep the temperature constant at 46°C for 30 minutes. This temperature has been shown to maximize the immunological response [5] and ensure a complete cell death within the targeted area [6].

2.

Previous findings in rat and man

Immunological events following imILT has been studied extensively. imILT is capable of inducing abscopal effects as demonstrated in a rat model of colorectal cancer in the liver [7], in which one of two simultaneous tumors was treated and anti-cancer effects were observed on both tumors. Long-term anti-tumoral memory effects has been demonstrated after imILT in the same model system, indicating an in situ "vaccination" [8]. Metastasis following imILT of the same rodent tumor model is lower compared to surgical resection [5].

Locally, imILT treatment causes increased numbers of macrophages to be recruited to the site and are observed both as ED1/ED1 positive cells in rat [8] and CD68 positive staining after treating breast cancer in humans [9]. ED1 positive cells are activated and stain positive for HSP70 [10]. Clinically activation of antigen presenting cells such as dendritic cells can be seen as CD83 positive cells [9]. As expected, proliferation of lymphocytes in the draining lymph nodes was demonstrated in vivo [11]. Lower numbers of CD25/FoxP3 positive regulatory T lymphocytes, in many studies associated with beneficial outcome, were noted clinically in the lymph nodes after imILT treatment. Going full immunological T lymphocyte response, one week after imILT treatment resection material show increased cytotoxic CD8 positive T lymphocytes in the tumor compared to pre-treatment biopsies [9]. These findings of increased numbers of cytotoxic T lymphocytes are also seen pre-clinically as well as an influx of $CD4^+$ T helper cells in the tumor after imILT treatment [8].



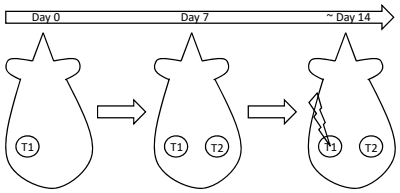
3.

Current investigations in mouse

Equipment and procedures have been adapted for use in mice, which are smaller and have correspondingly smaller tumors than rats. Subcutaneous tumor location was chosen in the mouse. This required changing from a bare end fiber used during the experiments in rat to a radial emitting fiber during the experiments in mouse.

Several tumor models have been evaluated. In order to study imILT-induced abscopal effects, the general experiment set up consisted in subcutaneous inoculation of tumor cells in the left flank (T1) as illustrated in the drawing below. Seven days later a second tumor of the same cell type was inoculated on the right flank (T2). When the first tumor (T1) reached about 100 mm^3, it was imILT treated, and the growth of both tumors were continuously recorded. Untreated T1 served as negative control.

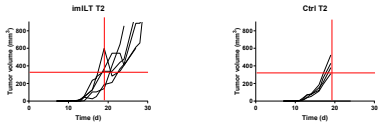
In a second set of experiments, the immunological memory was investigated. Tumors were inoculated subcutaneously on the left flank (T1). When the tumor reached 100 mm^3, it was imILT treated. After 14 days another subcutaneous tumor was inoculated and the growth was recorded. Mice not inoculated with T1 followed by imILT treatment were used as negative control.



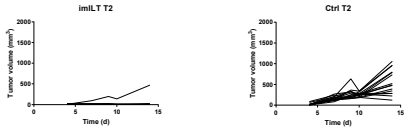
4.

Abscopal effects and immunological memory

Abscopal effect of the T2 tumor in the EG7OVA cell line is suggested from the data below. It cannot be fully proven in this initial experiment due to the low numbers per group (n=5), the short follow-up time and inadequate control group. Experiments are currently ongoing to further elucidate the abscopal effect using several cell lines.



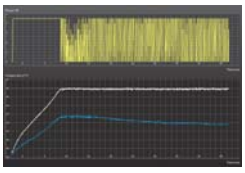
Re-challenge experiments were performed to study the long term effect on renewed tumor take. From the data below it can be concluded that imILT induces long term anti-tumor effects in the EG7OVA tumor model compared to naïve mice. Only 1/10 mice with previous imILT treatment showed take of a second tumor inoculation, while all 10/10 mice not previously imILT treated exhibited tumor take when subjected to a tumor inoculation.



5.

Clinical trials

Current studies aim to further elucidate clinical applicability of imILT treatment regime. Ongoing clinical trials studying imILT treatment in various types of solid tumors continue to generate valuable safety and efficacy data as well as operator usability information [12]. To the right is an illustration of a typical imILT treatment in a patient.



6.

Conclusions

- **Abscopal effects and immunological events following imILT treatment has been studied in different murine models of cancer, both in rat and mice.**
- **The presented data is the first data sets of the imILT laser protocol being used in a mouse model of cancer.**
- **Clinical studies of imILT are well underway in several tumor types such as pancreatic adenocarcinoma and malignant melanoma.**

7.

Selected references

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