**Continuous Low-Irradiation Photodynamic Therapy (CLIPT) for the Management of Cutaneous Metastases of Breast Cancer in Patients Failing Conventional Radiotherapy**

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**Introduction:**
Patients with cutaneous recurrences of breast cancer following mastectomy are conventionally treated with a combination of radiation therapy, chemotherapy, hormonal therapy, and/or surgery depending upon the size, location and receptor status of the metastases. A significant subset of patients develops further loco-regional progression of their disease despite high-doses of radiation therapy. Patients who have large surface area involvement or have received prior high dose radiation therapy to the same region to their chest-wall have few remaining therapeutic options.

In tissue culture and a murine model of glioblastoma, standard high dose-rate vs. continuous (5 days) low dose-rate (low-irradiance) photodynamic therapy (PDT) was evaluated (Bisland, 2004). Rather than losing or merely preserving efficacy of tumor response, the experiments demonstrated low-irradiance PDT enhanced tumor specific cell death, while minimizing injury to adjacent healthy tissue. Compared to high dose-rate PDT, both in-vitro and in-vivo data demonstrated a doubling of the rate of tumor cell specific apoptosis, with a thirteen-fold decrease in necrosis to healthy tissue when low-irradiance PDT was used (Bisland, 2004, Angell, 2006, Mathews, 2009). Based upon these promising pre-clinical data, we conducted the first-in-human (Phase I) trial of Continuous Low-Irradiance Photodynamic Therapy (CLIPT). We evaluated CLIPT in a patient population with cutaneous metastases from breast cancer that had failed surgery and radiation therapy. The primary endpoint was to determine the maximal tolerated dose (MTD) of 630nm laser energy that did not result in ulceration of previously irradiated normal skin adjacent to the tumor. Secondary endpoints included tumor response to CLIPT and quality-of-life parameters. The study was funded by the Susan Komen for the Cure® Foundation, received IRB approval and it is listed on the clinicaltrials.gov website.

**Materials/Methods:**
Adult subjects, 18 years of age and older, with 1 or more cutaneous nodules from locally recurrent and/or metastatic breast cancer were recruited for study enrollment. All subjects had to have failed conventional surgery and radiation. Participating subjects needed to be off any systemic anti-cancer therapy for 30 days prior to enrollment. Subjects with medical conditions associated with photosensitivity, pregnant or nursing, and those with severe hepatic dysfunction were also excluded.

**Study Design:**
The initial study design planned for sequential cohorts of 6 subjects to be treated at increasing laser intensity, starting at 100 J/cm² administered continuously over 24 hours (irradiance of 70mW/cm²). This starting point was considered well below toxicity as standard PDT for breast cancer utilized 150-200J/cm² administered over approximately 20 minutes (7,500 – 10,000mW/cm²). Dose limiting toxicity (DLT) was defined as partial or full thickness skin necrosis or pain not controlled with oral narcotics. The MTD was defined as the highest dose level at which < 33% of subjects experienced the DLT (2 of 6 subjects). The dose escalation algorithm determined that if 1/3 of the cohort subjects demonstrated DLT, the dose would be reduced by 50% for the following cohort. If < 1/3 of the cohort subjects experienced DLT, the treatment dose would be doubled for the following cohort.

Informed consent was obtained from all subjects. On the first day of study participation, subjects were given an intravenous injection of Porfirmer sodium (Photofrin®) at a dose of 0.8mg/kg body weight. Following a wash-out interval of 48 hours, subjects were admitted to the Clinical Research Center at Tufts Medical Center in Boston, MA. The target site was selected and marked by the principle investigator (PI), and a corresponding area of normal peri-umbilical skin served as the control site. Both sites were then covered with separate Light Patches. A Diomed 630nm PDT laser was coupled to each
Light Patch and calibrated for 24 hour treatment. Subjects then underwent 24 hours of continuous photodynamic therapy. Routine care and vital sign assessments were performed every 4 hours by a trained research nurse. On post-treatment day 1, a skin biopsy was done to assess histopathologic response, and a TUNEL assay was done to further evaluate the effects of therapy (Samples processed by the Study Center on the Immunogenetics of Infectious Disease at Tufts University School of Medicine). Subjects were then evaluated at post-treatment days 1, 7, 30, 60, and 90 for clinical tumor response, adverse skin reactions, evidence of systemic toxicity, and quality of life measures.

Results:

Fourteen subjects were enrolled in this study: 12 subjects with chest wall recurrence of breast cancer following mastectomy and two subjects with locally metastatic skin cancers that had failed surgery and radiation; a Merkel cell carcinoma of the left arm and cutaneous squamous cell carcinoma of the scalp in a heart-lung transplant patient. On completion of the intervention and after removal of the Light Patch, all 14 subjects were found to have punctuated ecchymosis, with moderate erythema and mild edema at the designated treatment sites. The control sites demonstrated only mild erythema without edema or ecchymosis in all subjects and was fully resolved by day 7. Eight of 14 (57%) subjects required narcotics during treatment, although none required further pain management 48 hours following completion of CLIPT. There were no malfunctions of the LDD.

The first 2 subjects were treated at 100 \( \text{J/cm}^2 \), and both experienced extensive tumor necrosis with skin ulceration occurring within 7 days of completing treatment. Subject #2 discontinued treatment after 10 hours due to pain (7/10), although she declined narcotics as an option for pain control. Since the DLT was experienced by both subjects, the stopping criterion (2 of 6 developing an adverse event) was reached and the subsequent subjects were dose reduced and treated at 50 \( \text{J/cm}^2 \) over 24 hours.

Six subjects (subjects 3-8) were enrolled in the second cohort and treated at 50J/cm\(^2\). None of these subjects (0/6) suffered partial or full thickness skin ulceration or necrosis or severe pain, thereby establishing the MTD at 50J/cm\(^2\). An additional 6 subjects (subjects 9-14) were treated at the MTD. Subject 11, an elderly man with metastatic Merkel cell carcinoma of the forearm who had failed surgery and radiation, was enrolled for compassionate use. He developed skin ulceration, later evolving to full thickness necrosis. Interestingly, his wound healed fully within 60 days and remained disease-free for over one year when he died from an unrelated event. Subject 14 received the intervention in 2 fractions of 12 hours administered on 2 consecutive days.

A robust clinical response was observed in our subject sample: 70% demonstrated either a complete (2/14) or partial clinical response (8/14), although the response was short-lived in the first 2 subjects (subjects 1-2) treated at 100 \( \text{J/cm}^2 \). Specifically, both subjects in the initial cohort developed new metastatic nodules within the treatment field 6-12 weeks following treatment, while none of the subsequent 9 subjects treated at 50 \( \text{J/cm}^2 \) recurred in the treatment field during 6 months of follow up. Of the 8 subjects (subjects 3 to 10) whose TUNEL assay results were available, 8 (100%) demonstrated a response to treatment as evidenced by either tumor apoptosis or regression on histologic analysis. Quality of life measures were also significantly improved, with a majority of subjects (10/14) reporting resolution or significant amelioration of bleeding and pain from tumor nodules. Two subjects (both partial responders) demonstrated regression of tumor nodules at a site distant from the treatment field.

Subjects 12-14 were treated with an untethered Light Patch comprised of a wearable power supply and light emitting 630nm bandage and funded by NIH grant 1R43CA139644-01A1. This new Light Patch enabled the subject to be fully ambulatory during the 24h CLIPT intervention. Subjects 12-13 were treated at the MTD with partial tumor response clinically and by TUNEL assay. Subject 14 was treated at 50\% of the MTD with no tumor response noted. Subjects 12-14 were partial responders in the Komen
funded phase of the study and developed new tumor nodules adjacent to the intervention site. No adverse reaction was noted in the overlapping skin that received the additional CLIPT session.

**Conclusions:**
This was the first-in-humans evaluation of continuous low irradiance photodynamic therapy (CLIPT). The Light Patch is safe to be worn on the skin and effectively delivered the proper energy for treatment. The MTD of CLIPT was determined to be 50J/cm² administered over 24 hours, however, the MTD on anatomic locations other than the chest-wall may be lower (based on 1 subject who developed full-thickness ulceration at 50J/cm² on the arm). Our data suggests CLIPT may be an effective therapy for the treatment of chest wall recurrence of breast cancer in patients who fail surgery and radiation therapy and should be evaluated in larger-scale studies. The majority of subjects experienced a durable clinical response defined as > 50% reduction in visible tumor burden for > 6 months. Based on 3 subjects, repeating CLIPT over time appears safe and effective. The majority of subjects reported significant improvement in their quality of life as measured by pain and/or bleeding parameters.


In our study, 1 of 13 subjects treated at the MTD of 50 J/cm² developed full-thickness skin ulceration. The MTD may vary with anatomic location and tumor type treated. The recurrence was located on the medial forearm, a location notable for a more limited blood supply than the chest wall. The Light Patch treatment field also encompassed approximately 50% of the arm circumference, leaving a limited amount of uninvolved extremity. Merkel cell carcinoma is a more vascular tumor than breast cancer, allowing for greater accumulation of photosensitizer and oxygen. This may have possibly accounted for the more exuberant response noted in this subject from the generation of reactive oxygen species (ROS). Of note, the control site on the subject’s thigh did not demonstrate an adverse reaction to treatment; only mild erythema at 24 hours and fully resolved by day 7.

Evidence from animal models using metronomic-PDT demonstrated a two-fold enhanced tumor specific cytotoxicity with decreased damage to healthy tissue when compared with acute-PDT (Bisland, 2004, Lilge, 2000). The mechanism for this improved tumor cell death may be related to the different rates of oxygen depletion and photobleaching of the sensitizer. High-irradiance (acute) PDT rapidly depletes oxygen and photosensitizer, with a subsequent loss of the ability to generate ROS (Agostinis, 2011, Bush, 2009). Once the drug and oxygen are depleted, the remaining energy simply causes non-specific thermal injury to all irradiated tissues. The 630nm light delivered at a low dose-rate reduces the rate of energy transfer from the photosensitizer and therefore slows the process of oxygen depletion; the tumor-specific effect is maintained for the 24-hours of therapy. Tumors, particularly like those in the CLIPT study which have failed conventional radiation therapy, tend to be relatively hypoxic, with a decreased potential to generate ROS. Continuous longer-term therapy is a more attractive option than a single, high-dose treatment, as the oxygen supply, and therefore the source of ROS, is not depleted as quickly. Similarly, there is less photo-bleaching of the sensitizer and, due to the prolonged time of treatment delivery, there is enhanced clearance of the photosensitizer from normal tissue (Agosinis, 2011).

Our complete response rate for recurrent breast cancer were less than those seen using conventional PDT (20% vs. 64% and 89%) (Cuenca, 2004, Allison, 2010). This may be due to small sample sizes (11 vs. 14 vs. 9 subjects, respectively) or that the CLIPT treatment may need to be extended or repeated (Cuenca, 2004, Allison, 2010, Mathews, 2009). Cuenca and colleagues treated a series of 14 subjects with chest wall progression of breast cancer at a fluence of 1800mW and a total light dose of 200 J/cm² in a single
outpatient procedure. They identified a complete response rate of 64% and, as in our study, also saw regression of tumor nodules distant from the treatment field (Cuenca, 2004). The high frequency of wound complications (necrosis was seen in all subjects) and the need for protracted wound care suffered by their subjects, however, would preclude it being used on a repetitive basis (one subject required surgical closure by flap creation, and another subject remains with an open wound at 21 months of follow-up). In a similar study by Allison, 9 subjects were enrolled and a total of 102 lesions treated (Allison, 2010). Using a light dose of 170 J/cm², with treatment delivered over 6 hours (a cumulative dose similar to that used in the CLIPT study); a complete response rate of 89% was reported. The authors described the post-procedural wound bed as typically “black and necrotic” with “erythema and edema in the entire illuminated light field.” The exact extent of tissue necrosis is not mentioned, although the authors describe the wounds as being “crusted over by either scab or eschar formation” by 2 months (with one subject requiring 14 weeks for wound healing). Five of 9 subjects also complained of severe chest wall pain requiring narcotics for 1-3 weeks post-treatment (Allison, 2010). This difference in response rates may have been partly due to the definitions used, as we defined a complete response as the clinical resolution of all tumor nodules rather than the per cent of individual nodules that disappeared following treatment. The advantage of CLIPT is the ability to provide multiple and repetitive treatment sessions due to its lower morbidity profile.

An interesting observation, also reported in other studies using PDT, was the effect on disease outside the treatment field. In our study, two subjects exhibited complete resolution of skin nodules outside the treatment field. This effect has also been reported with conventional ionizing radiotherapy and is referred to as the, “abscopal effect”. The abscopal (ab-scopus, away from the target) effect is a term used to describe radiotherapy-induced tumor regression in lesions distant from a targeted site, and has been known for six decades as a rare unexplained phenomenon in patients receiving local radiotherapy (Mole, 1953). It is hypothesized that the abscopal effect may result from a radiotherapy-induced immunogenic type of cancer cell death capable of generating an in situ vaccine (Drake, 2011). Although a small data-set, 20% of the subjects experiencing this effect is 3 orders-of-magnitude greater than reported after conventional ionizing radiation. We hypothesize that the enhanced abscopal effect may be a function of CLIPT primarily inducing tumor apoptosis rather than tumor necrosis that is seen with ionizing radiation and standard high-dose PDT. Larger clinical trials will verify if CLIPT enhances the abscopal effect and if it can be further improved with the use of an anti-CTL antigen-4 (CTLA-4) monoclonal antibody such as ipilimumab (Weber, 2012).

A major limitation of our data and the published studies on the role of PDT for cutaneous progression of breast cancer is the relatively small number of subjects treated. To address this problem, we have initiated a multicenter Phase II trial to evaluate the role of CLIPT as a treatment option for patients with cutaneous recurrence of breast cancer that have failed standard radiation therapy. Should our results be supported by the Phase II clinical study, CLIPT may be a viable option for managing patients who have failed standard therapy. As the energy is non-ionizing and this binary therapy can be delivered at very low morbidity, it can be used repetitively as a series of treatment sessions (fractionation) and repeatedly over time should new lesions develop. The Light Patch is wearable and can be used in an ambulatory setting, enabling the possibility of one day treating patients in underserved communities or who are geographically isolated and cannot travel to technologically advanced radiation facilities.

References:


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