Photomedicine and Laser Surgery
Volume 30, Number 9, 2012
© Mary Ann Liebert, Inc.
Pp. 551–558
DOI: 10.1089/pho.2011.3186

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A Preliminary Study of the Safety of Red Light Phototherapy of Tissues Harboring Cancer

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Abstract

Objective: Red light phototherapy is known to stimulate cell proliferation in wound healing. This study investigated whether low-level light therapy (LLLT) would promote tumor growth when pre-existing malignancy is present. ***Background data:*** LLLT has been increasingly used for numerous conditions, but its use in cancer patients, including the treatment of lymphedema or various unrelated comorbidities, has been withheld by practitioners because of the fear that LLLT might result in initiation or promotion of metastatic lesions or new primary tumors. There has been little scientific study of oncologic outcomes after use of LLLT in cancer patients. ***Methods:*** A standard SKH mouse nonmelanoma UV-induced skin cancer model was used after visible squamous cell carcinomas were present, to study the effects of LLLT on tumor growth. The red light group ($n=8$) received automated full body 670 nm LLLT delivered twice a day at 5 J/cm^2 using an LED source. The control group ($n=8$) was handled similarly, but did not receive LLLT. Measurements on 330 tumors were conducted for 37 consecutive days, while the animals received daily LLLT. ***Results:*** Daily tumor measurements demonstrated no measurable effect of LLLT on tumor growth. ***Conclusions:*** This experiment suggests that LLLT at these parameters may be safe even when malignant lesions are present. Further studies on the effects of photoirradiation on neoplasms are warranted.

Introduction

Low-level light therapy (LLLT) is being used increasingly for the treatment of a variety of conditions including trauma, wound healing, arthritis, musculoskeletal disorders, and dental and cosmetic applications.[1–4] The current therapeutic approach is to be cautious of potential harmful effects from the use of LLLT in patients with cancer. Its use for the management of lymphedema and other complications in cancer patients has been withheld because of the fear that LLLT might promote metastasis.[5,6]. This approach is summarized by the review of Hawkins et al., which stated that "LLLT should be avoided or given with special caution in…patients with cancer if there is any doubt of a recurrence of metastases.…Although LLLT has not induced cancer in any of the reported studies, the precise reactions of existing tumors to LLLT are unknown."[6] There is little scientific evidence available as regards oncologic outcomes and local responses to LLLT in cancer patients. Although it is unlikely that LLLT would induce *de novo* cancer development as there is no evidence that LLLT causes DNA damage, its effects on cellular proliferation have been the empiric basis for withholding treatment in cancer patients.

Red light is known to have a mitogenic effect based on its ability to activate cell division at certain spectral and dose ranges *in vitro*.[7–9] We are aware only of two studies on the effects of LLLT on cancer.[10,11] Revazova demonstrated the acceleration of tumor growth by 633 nm laser irradiation at 3.5 J/cm^2 three times per week for 2 weeks in a model of human gastric adenocarcinoma transplanted into immunodeficient athymic nude mice.[11] This suggests that LLLT is indeed capable of activating tumor growth under conditions that exclude immune resistance. In another study, the irradiation of squamous cell carcinomas (SCC) in the hamster cheek pouch with 660 nm light at 56 J/cm^2 and a 3 mm spot caused significant progression of the severity of SCC as judged by histology.[10] The bulk of literature on the topic of LLLT and cancer does not address the question of LLLT effects on tumor growth.

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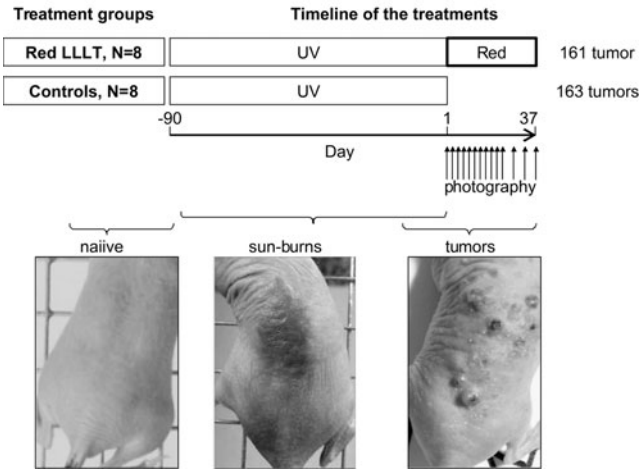

FIG. 1. Treatment groups and the timeline of the treatments. All the mice received UV light treatment for 90 days. By that time they already had developed the first tumors. At that point they were divided into two treatment groups matched by overall tumor area per mouse. Next day the red light irradiations were started for one group ("red LLLT") and photography was started for both groups. Typical photographs are shown here.

The present study investigated the potential promotion of tumor growth by LLLT cause by the stimulation of cellular proliferation in cancerous cells. A standard nonmelanoma mouse skin cancer model was used to test the effect of automated full body photoirradiation twice a day at 670 nm and at an energy density 2.5 J/cm^2 on tumor growth in already developed lesions.

We hypothesized that the systemic effects of phototherapy with red light might offset activation of cell division observed *in vitro*.

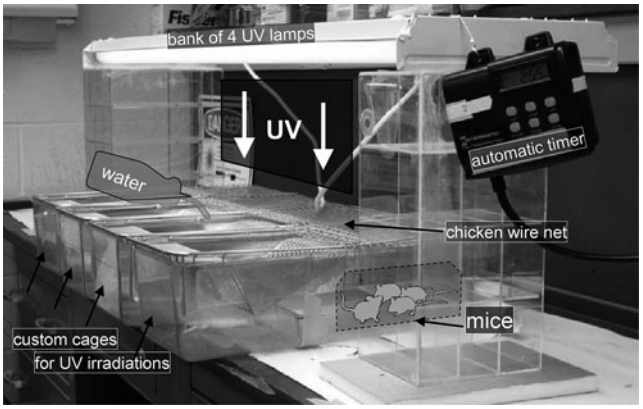

FIG. 2. Setup of UV irradiation. A bank of four UV lamps was installed 38 cm above the cage floor delivering 0.023 mW/cm^2 UVB and 1.4 mW/cm^2 UVA and was automatically turned on and off by an electronic timer. The cages were modified by combining 1 full and 2/3 of standard cage boxes together. The cover was replaced with chicken wire net to pass UV light, and the metal insert holding food and water was shifted as shown to avoid shading the mice from UV. This arrangement allowed servicing the mice only for examinations, cage cleaning, food, and water changes.

Methods

Irradiations

A standard skin cancer model, as described by Pentland et al.[12] was used under an Institutional Animal Care and Use Committee (IACUC)-approved animal protocol at Rochester General Hospital. Hairless SKH1 mice are healthy and have normal immunity and no melanin. Sixteen 4-week-old female SKH1 mice (Charles River Laboratories, Raleigh, NC) were housed four per cage for 1 week before UV-irradiation (Fig. 1). Cages were modified to make the mice accessible to UV light exposures. The food holder and the water bottle were shifted away (Fig. 2) to prevent the mice from hiding. The 295–390 nm UV light source consisted of a bank of 4 UVA340 lamps (QLab Corporation, Westlake, OH) installed in a generic fixture. Fluence was measured using IL1700 meter (International Light, MA) with SED240/UVB probe (detection range 255–320 nm) and SED005/UVA (315–390 nm). The UV exposure regimen was controlled by generic lawn-watering timers. The mice were UV-irradiated for 3 months; at three times per week (Monday, Wednesday, and Friday) and with 180 mJ/cm^2 UVB delivered fluence per session. UV exposures were increased by 10% each week. The cumulative dose was 12 J/cm^2 (UVB) and 658 J/cm^2 (UVA). Cages were rotated to keep all mice moderately sunburned (Fig. 1, middle). Excessively sunburned mice had reduced UV exposure to keep sunburn under 10 cm^2. UV was discontinued at 3 months. The mice were divided into two groups ($n=8$) matched by tumor area. Red light treatment was assigned to one of the groups by flipping a coin.

Red light treatments were started following the last day of UV irradiation. The custom cage setup for red irradiation is shown in Fig. 3. The 670 nm red light NASA LED arrays

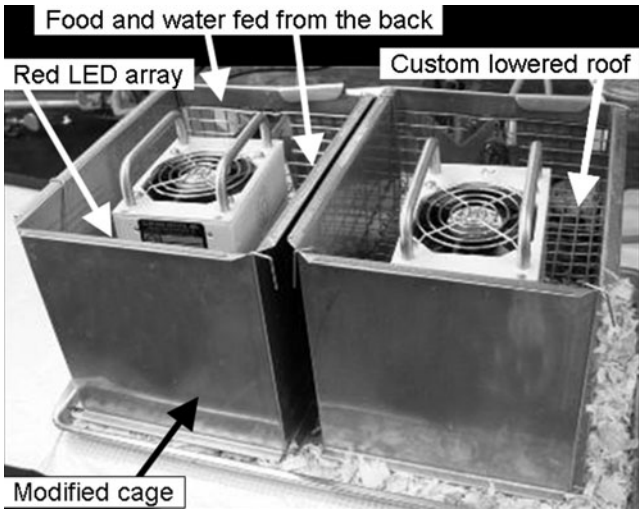

FIG. 3. Setup of red light irradiation. Two 670 nm LED arrays were powered by one power supply and automatically turned on twice a day for 6 min. Standard metal cages were modified by lowering the chicken wire roof to provide maximum intensity of red light without touching the mice. The uniformity and intensity of the irradiation was helped by the reflection from the inner walls. Note that enough of visible light penetrates through the roof allowing for the normal daylight cycle. The control cages had sham LED array inserts.

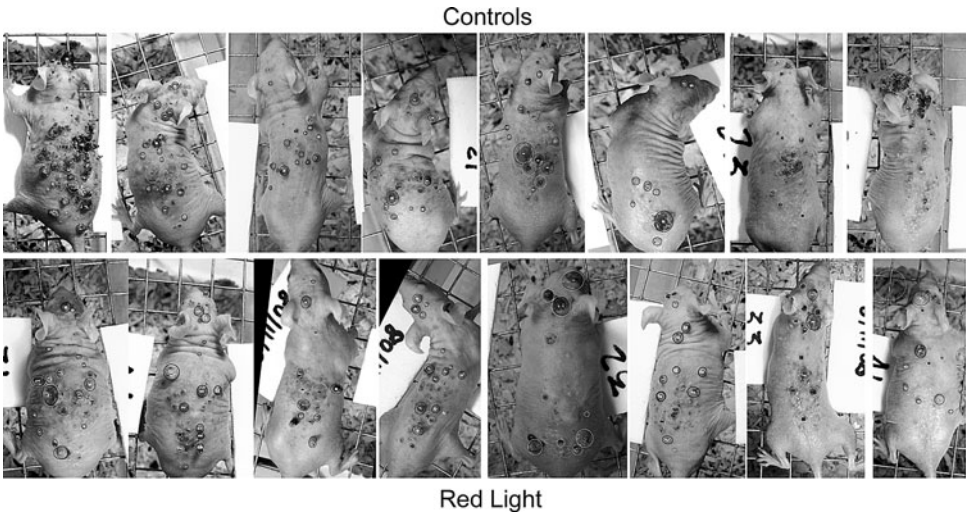

FIG. 4. Photographs of all mice on day 18, the day when a difference was observed in relative tumor area. Within each group, the mice were sorted by total tumor area from left to right.

(SpectraLife System, Quantum Devices, Barneveld, WI), composed of 91 hybrid gallium-aluminum-arsenium (GaAlAs) light emitting diodes each[13] (or sham arrays for controls), were laid flat on the wire grid roof. Measurements of the fluence with Newport 835C Power meter equipped with an 818SL detector head (Newport, Irvine, CA) showed high uniformity of illumination across the cage. The treatment group was irradiated automatically twice daily for 37 days at 8 mW/cm^2 fluence for 312 sec per session, resulting in a total dose density of 2.5 J/cm^2 per session, which corresponds to 5 J/cm^2 per day. We aimed to maximize healing and activation effects while avoiding inhibitory effects of red light. We selected the red light dose and fluence very conservatively based on prior work from our laboratory.[13] The chosen regime is in general agreement with the one used by Erdle et al.[14]

Photometry

Photographs were taken with a Nikon camera and enhanced with Thumbsplus (Cerious, Charlotte NC). Wire grid pitch was used to calibrate and save the scale using ImageJ (http://imagej.nih.gov). The area of each tumor was measured by manually circling it with the oval tool in ImageJ by an investigator blinded to the treatments. The contours were saved into the TIFF file over the mouse image to prevent counting tumors twice. Each tumor was measured across all time points first, and only then was the next tumor measured. Steps between measurements were semiautomated with MacroScheduler (MJTNet, Shaftesbury, UK). Graphing and statistics were done using Prism (GraphPad, La Jolla, CA). Curve fitting was done in Matlab.

Results

Treatment groups and irradiation schedules

All mice were subjected to 3 months of UV carcinogenesis (Fig. 1). UV-induced sunburns appear on day 3 of UV irradiation. Tumors started appearing 2.5 months after the start of UV and continued to appear throughout the duration of the study. Mice were divided into two groups matched by the total tumor area, and moved to the red light irradiation cages following UV induction. Red light irradiations were started the next day ("day 1") and continued twice daily for 37 days. The treated group mice received two treatments per day of full body 670 nm ambient red light from LED arrays at 8 mW/cm^2 fluence for 312 sec per session, resulting in a total dose density of 2.5 J/cm^2 per session (5 J/cm^2 per day).

Tumor counts

The tumors were photographed during the 37 days of the red light therapy and their area was measured on the photographs across time (Fig. 4). Each tumor was traced separately across time to maximize the power of the statistical analysis (Fig. 5). The counts of tumors >2 mm diameter are shown in Fig. 6.

Tumor area

As illustrated in Fig. 4, tumor sizes were heterogeneous in both groups on any day of the analysis. Figure 7 shows a histogram of tumor counts for different tumor sizes (areas) averaged across time. No statistically significant differences between treatment groups were observed. Tumor area was also plotted across time (Fig. 8). No statistically significant differences were determined by repeated measures ANOVA.

Transitory epidermis thickening

On days 2 through 4, the effects of the therapy were apparent in an unexpected way. The skin of the treated mice was observed to become much lighter in color and the texture was observed to be shinier, glossier, more reflective, and less transparent than the skin of the control mice. Control mouse skin textures were redder, darker, matte, and rough. The overall impression of the skin was that the red-light-treated mice had healthier skin, whereas the controls were still exhibiting the negative effects of damage from UV irradiation. The effect was strong to the extent that an investigator blinded to the identity of the mouse cages was able to guess correctly which cages were treated with red light based on the appearance of the mice. However, this effect ceased to be visible at later time points. It is possible that red light was inducing proliferation of keratinocytes in the epidermis, making it thicker.

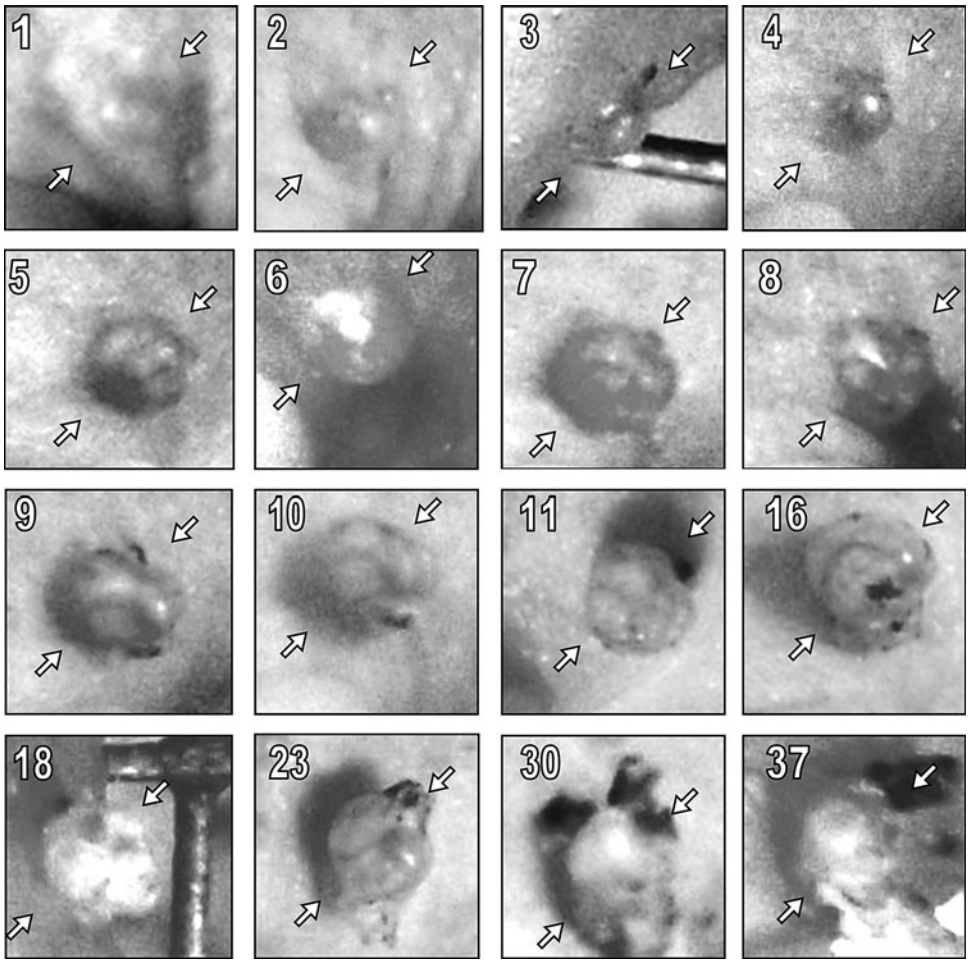

FIG. 5. An example of the growth of an individual tumor across time. Numbers are days from the beginning of the red light therapy. Arrows indicate 2 mm distance.

Improvement of vital signs

On days 30 and 37 of red LLLT, healthier behavior was observed in the red-light-treated group than in the controls. The treated mice moved normally; demonstrated normal posture; and exhibited active grooming, feeding, and drinking.

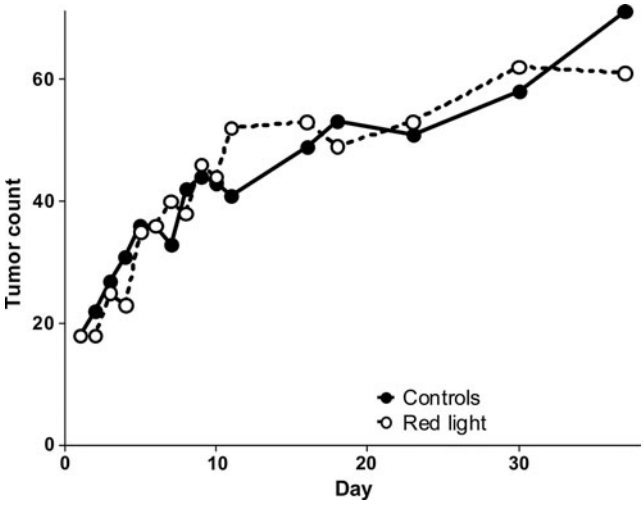

FIG. 6. Tumor counts across time.

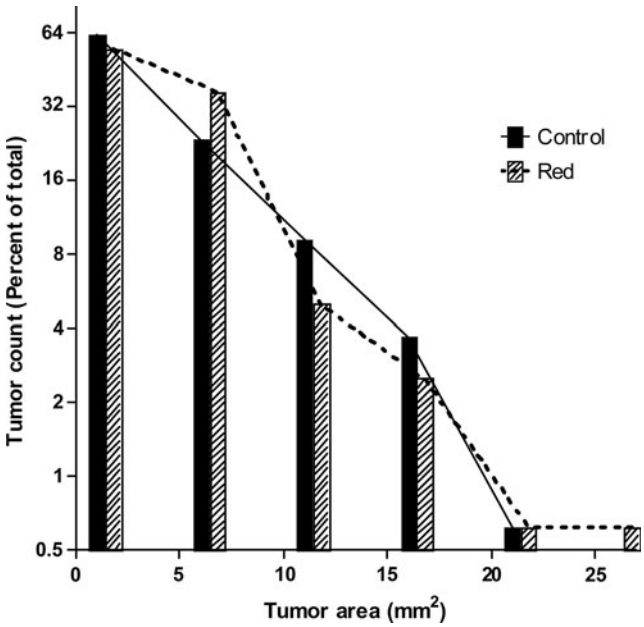

FIG. 7. A histogram of frequency distribution of tumor areas in the two treatment groups: red light LLLT and controls. An average area for each tumor across time was used. No statistically significant difference was observed between treatment groups for any tumor area.

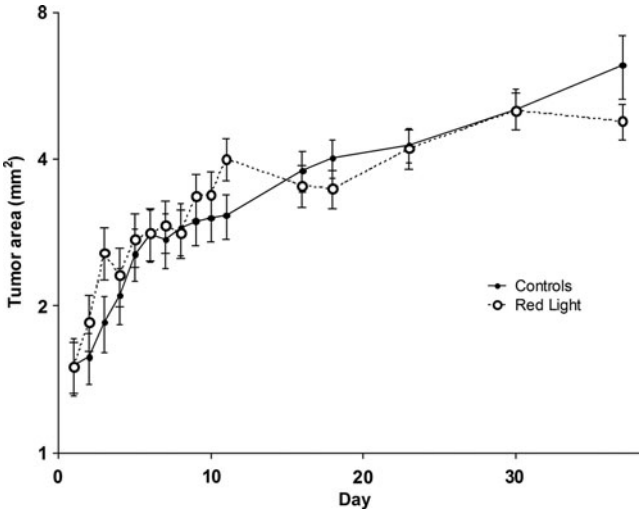

FIG. 8. Tumor area measured across time. No statistically significant difference was observed by repeated measures ANOVA. Mean ± SEM is shown.

The control mice showed typical sickness behavior including a semicollapsed posture, shivering as a sign of being cold, lack of movement, and lack of grooming. This observation is consistent with our earlier report of beneficial effects of LLLT on immune response and sepsis.[15]

Discussion

The use of phototherapy in the treatment of cancer patients has been controversial. Current recommendations suggest that therapy should be carefully considered and used cautiously in patients with cancer, and that treatment in areas bearing tumors should be avoided. This empiric advice is based on our current knowledge of the experimental acceleration of cellular proliferation and stimulation of wound healing and tissue repair as demonstrated in both animal models and clinical scenarios.[16–18]

There have been few studies that have investigated the influence of LLLT on tumors and tumor growth. The hamster cheek pouch DMBA-induced oral SCC has been recently investigated by Monteiro et al.[10] The authors treated the oral cavity with 660 nm LLLT after induction of tumors. Histological evaluation demonstrated an increase in the progression and severity of SCC.[10]

Liebow et al. had also demonstrated an apparent stimulation of tumor induction and growth after CO_2 laser incisions were created in cheek pouch tissue that had been transformed as a result of DMBA painting.[19,20] Both the Montiero and Liebow investigations involved manipulations of tissue that had been manipulated into a transformed field as a result of DMBA induction. This process inevitably results in tumor formation and it is well known that scalpel incisions and other perturbations of the epithelium can stimulate tumor induction. It is also well known that these tumors are dependent upon epidermal growth factor (EGF) for growth.[21] Saliva contains significant concentrations of EGF and other growth factors and cytokines. Inflammation results in consumption and degradation of these growth factors, and processes that reduce or modulate the inflammatory response similarly affect tumor development in these tissues. CO_2 laser use results in a reduction and delay in the inflammatory response.[22–25] This particular laser is capable of inducing heat shock proteins by a mechanism similar to that observed in modification of wound healing and scar formation in laser-assisted-scar-healing (LASH) in humans.[26,27] Similarly, phototherapy at 660 nm is known to reduce inflammation.[28]

Both of these studies demonstrate that the local milieu is important in the induction and proliferation of malignant lesions. However, it would not be appropriate to make generalizations about all types of cancers based on this very specific model and tumor system.

The model

We chose a model that can produce a large number of malignant cutaneous lesions economically and automatically (Fig. 2), provides a way to irradiate them with red light automatically (Fig. 3), and allows us to monitor the growth of these tumors daily. This experimental model (Fig. 1) induces spontaneous and genetically heterogeneous nonmelanoma skin cancers on the backs of hairless mice after UV damage. The induction of cancer by UV exposure is a random process and involves a combination of randomly induced mutations in multiple genes per tumor. The tumors produced by this model are heterogeneous, which is more representative of a wider range of clinically observed cancers as contrasted to models that use genetically homogeneous cancer cell lines. Although nonmelanoma skin cancer is not as deadly as other cancers in humans, it is a true cancer genetically and functionally and therefore with the effects of red light, LLLT in the presence of these neoplasms is relevant to the potential effects of red light therapy on other types of cancer.

The advantage of SKH-1 mouse cancer model is that the cells producing cancer in the overwhelming majority are epidermal keratinocytes, that is the fast-dividing keratinocytes of the lowest layer of epidermis, which is very thin in mice, less than 0.05 mm. Therefore, the tumors grow on the surface of the skin and a very minor part of each tumor is below the surface.[29–33] Early investigations using the SKH-1 model documented the high degree of histologic similarity in the numerous cutaneous malignant lesions produced in this model.[29–33] In addition, the high throughput method of periodic photographing the tumors and measuring their diameter on the photographs, a well-established method of measurement, fosters the analysis of hundreds of tumors longitudinally, which is not possible with other end-point methods, such as histology. The majority of the research studies utilizing this SKH-1 cancer model use the size of the visible tumor as a function of time as a measure of tumor proliferation.[12,34–41]

The sensitivity of the model to detect small therapeutic effects is limited by the fact that the tumors in treatment and control groups are by their nature different genetically, as each tumor is a result of random mutagenic events. Although this difference is of no significance, because of large numbers of medium-sized tumors in both groups, the individual random mutations resulting in the induction of small numbers of large fast growing tumors potentially affected the overall statistical results. This limitation can be overcome in the future by increasing the number of mice treated or by

measuring baseline growth rates for each tumor before the beginning of red light therapy, and then comparing the growth rate of each tumor before and after beginning the therapy.

Automation and human interventions

We have developed a new method that uses a well-characterized animal model for the study of the effects of LLLT on cancer. The advantage of this model is that the setup minimizes the human factor, both in influencing mouse behavior and in data analysis. The mice are irradiated automatically and the tumors are sized across time using image morphometry blinded to treatment, thus excluding human bias.

Evidence supporting the safety of red light

This study aimed to maximize the healing and activation effects while avoiding the inhibitory effects of red light. We selected the red light dose and fluence very conservatively based on our prior studies on wound healing.[13] Treated mice received two irradiations per day at $8\,mW/cm^2$ fluence for 312 sec per session, resulting in a total dose density of $2.5\,J/cm^2$ per session ($5\,J/cm^2$ per day). This regimen is in general agreement with the one used by Erdle et al.[14] Erdle et al. used the same red light source and mouse strain (SKH-1), measured incisional wound healing, and demonstrated the high efficiency of chronic daily treatment at a dose of $3.6\,J/cm^2$ (either 450 sec at $8\,mW/cm^2$ or 37 min at $1.6\,mW/cm^2$).

This study documented the absence of strong positive or negative effects of LLLT on tumor growth in this model and red light treatment parameters. Prior studies using the same red LLLT system demonstrated that these parameters stimulate wound healing.[13] The present study provides some evidence that phototherapy at these parameters should not be empirically contraindicated in the treatment of patients with cancer. Our qualitative observations of improvement in skin quality at early time points, and relief of sickness behavior at later stages of the investigation, are also suggestive of the fact that the light was capable of producing beneficial effects for the whole animal despite the presence of tumors. It should be recognized, however, that the present study delivers, essentially, whole body therapy to the affected individual, rather than treating a specific area.

The small but statistically significant decrease in tumor area observed on days 16–23 demonstrates the ability of our model to detect small changes in tumor volume because of the low degree of random histotype variability in the model and the high number of examined tumors and time points. An additional explanation as to why red light was beneficial at days 16–23 may be the stimulation of antitumor immune activity or, perhaps, a local photodynamic effect as a result of red light activation of endogenous porphyrins present in tumors in and around areas of spontaneous hemorrhage and necrosis. Red light treatment was qualitatively observed to relieve sickness behavior, which suggests that there was an improved host response and increased antitumor immunity; at least until the tumor burden overwhelmed these effects. Future studies directed at studying these immune effects would be helpful in determining the biological basis for these observations.

Targets of the red light

Important factors to consider are: what tissues were reached by the red light during whole body phototherapy as was the case in this study, and which chromophores are absorbing the light. Because the mice have hairless fair skin, the light was not shielded by hair or melanin. The necrotic tissue covering some of the tumors might have shielded some tumor cells from the red light and/or may have generated local photodynamic effects caused by interaction with endogenous porphyrins. Much of the light likely did penetrate deeper in the mouse, potentially stimulating lymphatic vessels, lymph nodes, internal organs such as the spleen, and, possibly, even the bone marrow. It is likely that both actively dividing tumor cells and immune cells including white blood cells; immune cells infiltrating the skin such as mast cells, dendritic cells, neutrophils, and other, lymphatic vessels and nodes; bone marrow; and, possibly, spleen were absorbing and being activated by the light treatments.

As this study suggests that the outcome of red light therapy depends upon competition between possible activation of tumor growth on the one hand, and improvement of systemic antitumor immune response on the other, future studies should address the issue of local versus systemic red light therapy. Treatment was systemic in this case because of whole-body photoirradiation. Specific studies would be helpful, particularly if treatment can be isolated and directed solely to healthy tissues, both tumor-bearing and healthy tissue, or tumors alone.

Conclusions

The present study failed to demonstrate a harmful effect of whole-body red LLLT on tumor growth in an experimental model of UV-induced SCC. There was a transient and small reduction in relative tumor area in the treatment group compared with controls. This study suggests that LLLT should not be withheld from cancer patients on an empiric basis. Further investigations designed to build upon these observations and determine the mechanism for the host–tumor responses noted during the early treatment phase are warranted.

Acknowledgments

This work was performed at The Rochester General Hospital Surgical Laser Research Laboratory and funded in part by Quantum Devices (Barneveld, WI), and the Kidd Fund of the Rochester General Hospital Foundation. Dr. Myakishev-Rempel's research was supported in part by an NIH T32 AR007472 grant. We thank Drs. Alice Pentland and Francisco Tausk for their support and for sharing the material resources for these experiments. The LED sources used for this study were provided by Dr. Harry Whelan and the NASA Marshall Space Flight Center. We thank Prof. Lars Hode and Dr. Gerald Ross for their discussion and literature contributions.

Author Disclosure Statement

Dr. Myakishev-Rempel has been compensated for this work by Warp Photomedicine (Barneveld, WI). No competing financial interests exist for the other authors.

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