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A Retrospective Review of Pain Control by a Two-Step Irradiance Schedule During Topical ALA-Photodynamic Therapy of Non-melanoma Skin Cancer

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Abstract

Background and Objective—Photodynamic therapy (PDT) with topical δ-aminolevulinic acid (ALA) of non-melanoma skin cancers is often associated with treatment-limiting pain. A previous study on basal cell carcinomas (BCCs) at Roswell Park Cancer Institute evaluated a two-step irradiance scheme as a means of minimizing pain, preserving outcomes, and limiting treatment time. We used an initial low irradiance until 90% of the protoporphyrin IX was photobleached, followed by a high irradiance interval until the prescribed fluence was delivered. Success of this pilot investigation motivated integration of the protocol into routine practice. Here we present a retrospective review of recent clinical experience in a broad patient population.

Study Design/Materials and Methods—This was a retrospective review of an existing dermatology data base. Fourteen caucasion patients - 9 men and 5 women, ages 18 to 80, with a total of 51 superficial and 73 nodular BCCs, and three Bowen's disease lesions – were included. ALA was applied to each lesion for approximately 4h. Lesions received an initial irradiance of 30 - 50 mW/cm^2 for 20 J/cm^2, followed by 150 mW/cm^2 for a total fluence of 200-300 J/cm^2. Pain was assessed using a visual analog scale (VAS). Clinical outcome was determined at 6-12 months.

Results—Median VAS scores were 1.0 for both irradiances. Five of 127 lesions required pain control with 1% xylocaine. Pain was strongly influenced by lesion location but not by lesion type, number, or size. Complete responses were achieved in 84.1% of BCCs, which compares favorably with reported results for single ALA-PDT treatments. Two of three Bowen's disease lesions showed a complete response. Complete responses for nodular BCCs were 37%, which are also within the range of reported outcomes.

Conclusions—A two-step irradiance protocol in ALA-PDT effectively minimizes pain, maintains excellent clinical outcomes in superficial lesions, and adds minimal treatment time.

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Keywords

δ-aminolevulinic acid; basal cell carcinoma; Bowen's disease; protoporphyrin IX

INTRODUCTION

Photodynamic therapy (PDT) with δ-aminolevulinic acid (ALA) or its derivatives is finding widespread use as treatment for actinic keratoses (AK) and selected basal cell carcinomas (BCC), achieving high durable response rates and excellent cosmetic outcomes (1-3). The sole significant limiting effect of this therapy is the experienced pain during the therapy session (4-7). The pain can be severe, especially during treatments of multiple and/or extensive lesions. Local anesthesia, including nerve blocks and occasionally IV sedation or general anesthesia may be required depending on the number and location of lesions. Spray cooling of the lesion during irradiation, fractionated irradiation, and use of visible light plus water-filtered infrared A have also been explored as methods to reduce treatment-associated pain (3, 4, 8).

Topically applied ALA functions as a pro-drug that is converted intracellularly via the heme biosynthesis pathway to the photosensitizing agent, protoporphyrin-IX (PpIX) (1, 9). The latter is then activated by exposing the lesion to visible light of an appropriate wavelength. In the presence of tissue oxygen, light-activated PpIX generates cytotoxic reactive oxygen species, predominantly singlet oxygen (9). Light irradiance has emerged as an important treatment parameter; high irradiance can cause oxygen depletion in the presence of relatively high photosensitizer levels, thus reducing treatment efficiency (10-12)(13). Furthermore, the irradiance has been found to correspond with the kinetics of self-sensitized photobleaching of PpIX and the degree of pain experienced by the patient, with enhanced photobleaching as a function of fluence and significantly reduced pain at lower irradiance (14).

In a previous study performed at Roswell Park Cancer Institute (RPCI), a two-step irradiance schedule for the treatment of BCC was devised in an attempt to decrease the PDT treatment related pain without significant increase in treatment time (14). That study was restricted to BCCs of no more than 5-20 mm in diameter and to two lesions per patient. BCCs were irradiated initially at varying low irradiances (10-60 mW/cm^2) until 90% of the initial PpIX was photobleached, as determined by surface fluorescence measurements, with a subsequent increase of the irradiance to 150 mW/cm^2 for a total light dose of 200 J/cm^2. The two-step irradiance study revealed three major results: 1) photobleaching rates were enhanced under low irradiance, indicating more efficient PDT, 2) treatment outcomes were comparable to continuous 150 mW/cm^2 treatment, and 3) irradiation at irradiances below 60 mW/cm^2 caused no or minimal pain and, when preceded by low irradiance, 150 mW/cm^2 likewise caused no or minimal pain.

Following the completion of the earlier prospective RPCI study, patients were identified who had multiple non-melanoma skin cancers or lesions >20 mm and who were not eligible for an open study. Pain was expected to be a very serious issue in these patients because of the size and number of lesions. Transition of the two-step irradiance approach from research investigation to clinical use presented the solution. Thus, the earlier clinical research protocol information became the foundation for a two-step irradiance, off-label PDT approach for patients with multiple or large skin cancers. Treatment parameters were simplified to be attainable in general dermatologic practice. Both pain levels and clinical outcomes were recorded. The goal of this retrospective analysis was to assess the general

applicability of the two-step irradiance protocol to the ALA-PDT treatment of cancerous skin lesions.

METHODS

This is a retrospective off-label review of patients treated by the two-step irradiance approach between July 2007 and December 2011. All eligible patients were included in this review.

Patients

Patient and lesion characteristics are shown in Table 1. The patients were male or female, at least 18 years old, with a diagnosis of superficial or nodular basal cell carcinomas or Bowen's disease. Five patients suffered from nevus basal cell carcinoma syndrome (NBCCS). Except for the NBCCS patients' lesions, which were diagnosed clinically by a board certified dermatologist, lesions were verified histologically. Although some patients, especially those with NBCCS, had received ALA-PDT before, all lesions reported here were previously untreated. A limit of eight treatment fields per day, each field containing no more than four lesions, was adhered to, with no limit on lesion size or location. Treatment field diameters ranged from 1.3 to 5.4 centimeters. Eighty six percent of patients had multiple areas treated during one treatment session. All patients were offered surgery as alternative treatment but chose ALA-PDT because of its proven superior cosmesis.

Because 20% topical ALA-PDT is approved by the U.S. Food and Drug Administration only for the treatment of actinic keratoses, the reported treatments represent an off-label use of this treatment modality. In accordance with the FDA guidelines, patients were informed of the off-label nature of the treatment. All patients signed the required off-label procedural consent form.

ALA Administration

δ-Aminolevulinic acid HCl 20% in alcohol (ALA, Levulan® Kerastick, DUSA Pharmaceuticals Inc., Wilmington, MA) was applied to each lesion plus a ~1.0 cm diameter clinically disease-free zone surrounding each lesion. Lesions did not receive any specific preparation before ALA application. The ALA was covered by an occlusive dressing and black duct tape to prevent contamination, migration, and photoactivation prior to irradiation. The ALA remained on the skin for 4h ± 15% to allow for formation of the photosensitizing agent PpIX. The area was cleansed with normal saline prior to irradiation to remove residual cream. All lesions were evaluated for fluoresence using a Wood's lamp flashlight prior to treatment.

Irradiation

The PpIX activating light of 633 ± 3 nm was delivered superficially via an optical fiber coupled to an argon-ion-laser-pumped dye laser (ArDL, Coherent Innova 100+®, Coherent, Inc., Santa Clara, CA) to previously determined field size specifications. Light exposure consisted of two parts: the initial therapy was delivered at an irradiance of 40 mW/cm^2, with some selected lesions initially receiving 30 or 50 mW/cm^2, for a total of 20 J/cm^2. This was established in our earlier prospective study as the light dose where ~80-90 ± 10% of the initial PpIX fluorescence in the lesions is bleached (14). Specific PpIX photobleaching measurements, as performed in our earlier study (14), were not carried out as most dermatologic clinics would not have the ability to perform these measurements. In some patients/lesions the initial irradiance levels were adjusted up-or downward among 30, 40 or 50 mW/cm^2 during irradiation, depending on reported pain levels. After delivery of the 20 J/cm^2, the irradiance was raised to 150 mW/cm^2 until a total light dose of 200 or 300 J/cm^2

was delivered. An oscillating fan was utilized during all procedures to counteract the warmth generated by the treatment light. This did not appear to affect the patients' pain sensation.

Pain Assessment

Pain was assessed using an 11-point pain visual analog scale (VAS). Patients were advised that a sensation of warmth should be expected, were shown the pictorial VAS pain card, and levels of pain were discussed. None to low pain is defined as a VAS score of 0-3, moderate pain as 4-6, and severe pain as 7-10. Patients were questioned at the start of treatment and every 5 minutes thereafter about changes in pain and were advised to notify the staff of any changes in their pain at other times. For each irradiance, the maximum pain level was recorded. If pain was VAS ≥ 4, the irradiance was lowered by 10 mW/cm^2 and/or the lesion was injected with 1% xylocaine with 0.5 cc sodium bicarbonate if patients desired pain relief. A VAS ≤ 3 usually required no intervention. When the irradiance was changed to 150 mW/cm^2 pain was assessed and recorded in a similar manner.

Clinical Follow-up

Patients' lesions were evaluated at 6-12 months after a single PDT treatment. Because the treatment was off-label, patients were instructed to return to their primary dermatologists for additional follow up after that evaluation. Upon examination of the treated areas by the treating physician, a comparison was made to pretreatment photographs and sizes. Results were described as complete clinical response (CCR, 100% clearance), partial response (PR, >50% clearance), marginal response (MR, <50% clearance), and complete failure (CF, no response). For a lesion to be declared a complete clinical response, at least 6 months follow-up was required. Patients with responses other than CCR were either retreated with ALA-PDT or underwent surgery; these subsequent treatments are not included in this report.

Statistics

Analysis considered all lesions combined, regardless of the initial low irradiance. Wilcoxon Rank Sum tests were used to determine significant VAS differences based on gender, type of cancer, location, or number of areas treated. Kruskall-Wallis tests were employed for comparison of more than two groups. A value of ≷ was regarded as significant. Summary statistics for VAS pain score (categorical) were presented as counts and percentages for each category. Fisher's exact tests were used to assess the association between VAS pain scores and other factors. A value of $P < 0.05$ was regarded as indicating a significant association between VAS pain score and the factor of interest.

RESULTS

Patient Population

The characteristics of the patient population including gender, age, race, lesion diameter and lesion location are shown in Table 1. Fourteen patients, 9 men and 5 women, with a total of 127 distinct lesions, 51 superficial (sBCC), 73 nodular (nBCC) and 3 Bowen's disease, were treated. The predominant location of lesions was the trunk, followed by the head and neck, lower extremities and upper extremities. Fifty nine percent of lesions measured between 1-2 cm in diameter, 24% were between 2-3 cm, 16% were between 3-4 cm, and 1% were > 4 cm. The minimum number of lesions treated per patient was one (three patients), and the maximum was 74 (one patient treated in six treatment sessions).

Clinical Outcomes

Treatment Response—Forty-four of 51 sBCCs (86%), 3 Bowen's disease (100%), and all 73 nBCCs (100%) were evaluated for clinical outcome at ≥ 6 months follow-up. Seven sBCC lesions have not yet completed the evaluation time period. Of those completed, the CCR rate for sBCC was 84.1%, with 13.6% PR. One lesion did not respond (CF). Of the three Bowen's disease lesions, two were CCR and one was rated a PR, with ≥ 90% clearance. The CCR rate for nBCC was 35.6%, with 59.0% PR and 5.4% showing only marginal responses.

All patients were able to complete the treatments as planned. No adverse events occurred, and patients tolerated ALA-PDT without difficulty. Patients were able to resume normal activity in all cases within two to three weeks. Scarring if it existed was considered minimal. All patients experienced no functional impairments.

Pain Assessment—The initial irradiance in the majority of lesions was 40 mW/cm^2. In selected patients/lesions initial irradiances were 30 or 50 mW/cm^2 and were adjusted up or down according to reported pain levels and the physician's discretion. All patients received a high irradiance of 150 mW/cm^2 during the second treatment interval.

The median VAS scores for the 40 mW/cm^2 irradiance were as follows: patients with sBCC 1.0 (min 0.0, max 7.0); nBCC 2.0 (min 0.0, max 8.0); of the three Bowen's disease lesions, one was recorded as 3, the others as 0. Median VAS scores for the high irradiance portion following low irradiance (without analgesics) for sBCC were 2.0 (min 0.0, max 4.00) and for nBCC 1.0 (min 0.0, max 6.0). The Bowen's disease lesions were recorded as 4 (1 lesion) and 0 (2 lesions). Overall, the median VAS for all lesions combined was 1.0 (min. 0.0, max. 8.0) for low irradiance and 1.0 (min. 0.0, max. 6.0) for high irradiance. There was no statistical difference between the VAS scores for superficial or nodular lesion types.

Statistical analysis suggested no significant difference in low irradiance VAS scores between male and female patients but a significant difference (P<0.001) in high irradiance VAS scores between genders, with females reporting higher pain levels.

There was no statistical difference in VAS scores with regard to the number of lesions per patient. However, the location of the lesions proved highly significant (P<0.0001), with areas on the head and lower extremities most sensitive. Table 2 lists the location of all 24 lesions (in 11 patients) recording VAS>3 (moderate pain and higher) under irradiance of 40 mW/cm^2. Only 3 required downward adjustment of the irradiance. Of all 127 lesions treated at initial low irradiance, only 5 received xylocaine. Six lesions in 3 patients (3 sBCC, 3 nBCC) irradiated initially at 50 mW/cm^2 scored VAS 3 (1 lesion) and 5 (5 lesions). Upon adjustment of irradiance to 40 mW/cm^2, all VAS scores were reduced to 1. Conversely, in another patient the initial irradiance on a sBCC on the tip of the nose was chosen to be 30 mW/cm^2 based on the expected high pain sensation at this location. When no pain was reported at this irradiance, the irradiance was increased to 40 mW/cm^2, which caused severe pain (VAS 7). Pain persisted (VAS 5) even after a return to 30 mW/cm^2, and xylocaine was administered. One patient with two sBCC lesions on the face reported “intolerable” pain at the initial 40 mW/cm^2, which became “tolerable” upon irradiance decrease to 30 mW/cm^2; no specific VAS scores were obtained. Six of the 9 treatments started at 50 mW/cm^2 had to be adjusted downward.

After the initial light dose of 20 J/cm^2 was delivered, the irradiance was uniformly increased to 150 mW/cm^2 for the remainder of the treatment. Only seven of 127 lesions had a VAS increase to a level ≥4, with no xylocaine required.

DISCUSSION

The pain associated with the conventional PDT treatment for superficial cutaneous tumors using topical ALA and its derivatives is severe and can often be intolerable. The requirement of analgesics, and in the case of large and numerous lesions sometimes anesthesia, is a serious drawback of this otherwise highly useful therapy. Treatment has frequently been interrupted or abandoned due to pain. Therefore, a reliable, simple and inexpensive method to greatly reduce or eliminate pain associated with PDT using ALA and its derivatives represents significant clinical benefit.

This retrospective analysis of off-label treatments of topical ALA-PDT of cancerous skin lesions, which employed a two-step irradiance protocol to control light-treatment-associated pain, was carried out to assess the validity of this approach for the general dermatologic practice. The goal was to determine if we could fix the amplitude and the duration of the initial irradiance based on previous experience and still retain the benefits – pain reduction and treatment efficacy without significant increase in treatment time – without the complexity of performing real time optical measurements on each patient. The analysis has revealed that for most lesions an initial irradiance at 40 mW/cm^2 for 20 J/cm^2, followed by an irradiance at 150 mW/cm^2 for the remainder of the total required light dose, causes no or minimal pain. For lesions located close to bone or heavily innervated areas (H&N, tibia), an initial irradiance of 30 mW/cm^2 for 20 J/cm^2 is recommended. The light dose of 20 J/cm^2 for the initial low irradiance interval was adopted from our earlier prospective study because it had been found to photobleach 80-90% of PpIX. The elimination of direct monitoring of PpIX photobleaching during PDT for each patient was a critically important aspect of this study. The fact that treatment parameters derived previously appear to be generally applicable enables the protocol to be adopted widely by dermatologic clinics, few of which are capable of integrating spectroscopic monitoring into routine use.

An extensive review of pain associated with ALA-PDT for various skin diseases, including psoriasis, acne, actinic keratoses (AKs) and BCC, has been published by Warren et al.(4), covering 43 publications between 2000 and 2008. Pain usually commences immediately upon the irradiation of the lesion and tends to level off with time of light exposure. Treatment parameters such as PpIX fluorescence, wavelength of light, light dose and light dose rate have all been investigated with regard to pain, with often-conflicting results. Approaches to pain control have also been investigated and it was concluded that cooling of the lesion during irradiation was so far most effective, although this provided only limited relief (4).

The relationship between irradiance, which in the majority of published studies ranged from 50 to 150 mW/cm^2, and pain has been investigated in several studies. Ericson et al. (15) found no difference in pain levels between 30 and 75 mW/cm^2 in AKs treated with ALA-PDT. On the other hand, Wiegell et al. (16), using the ALA derivative (methylaminolevulinic acid (MAL), found significantly higher pain scores with 68 mW/cm^2 than 34 mW/cm^2 in patients with acne. In a randomized study of MAL-PDT for AKs, comparing pain levels with two different light sources (irradiances of ~50-75 mW/cm^2) and cooling sprays, von Felbert reported median pain levels of VAS 50-80, using a VAS scale of 0-100 (8). Cottrell et al. (14) demonstrated a clear relationship between irradiance and pain when using ALA-PDT and 633 nm wavelength irradiation in sBCC. Taking advantage of the fact that the origins of ALA/PDT-induced pain are photochemical rather than photothermal and exploiting the more efficient photobleaching of PpIX at relatively low irradiance (14), they devised an irradiation schema that employed low irradiance until 80-90% of PpIX was photobleached (within 3-8 min), followed by high irradiance until the full light dose (200 J/cm^2) was delivered. Starting irradiances below 60 mW/cm^2 resulted in

most cases in minimal pain throughout the treatment without the use of analgesics, and with good clinical responses. Our current retrospective analysis of this off-label use of ALA/PDT revealed remarkably low pain levels, with an overall median VAS score of 1.0 for both irradiance levels.

Since the goal of our report was to validate a two-step irradiance approach in the day-to-day clinical practice, with fewer restrictions on lesion size and number, irradiances in some cases were adjusted depending on the clinician's expectation based on prior experience, lesion location, patient's anxiety levels, etc. One caveat regarding these data is the fact that the number of lesions was not distributed evenly among patients, i.e. a few patients provided a large number of the evaluated lesions, which might have influenced the analysis. Nevertheless, the analysis confirms the low irradiance pain levels reported by Cottrell (14). We note, however, that in the current study, all but two of the lesions treated with an initial irradiance of 50 mW/cm^2 scored VAS 3 or higher, well above the median of 1, suggesting that a more reliable estimate of the pain threshold irradiance is closer to 50 mW/cm^2.

These exceptionally low pain scores may be somewhat influenced by the fact that, except for three Bowen's disease lesions, all lesions analyzed were BCCs. The type of skin disease treated has been shown to be a strong predictor of pain. Psoriasis likely produces the highest levels of pain (4, 17, 18) compared to other lesions. Thus, a different, lower initial irradiance may be necessary for ALA-PDT in these patients. Grapengiesser et al. (19) concluded that BCC's, which had a mean VAS score of 3.5 with irradiance of 76.5 mW/cm^2, generated less pain than AKs, although the field size treated was much larger with AKs than BCC's, possibly confounding any conclusion. In the current study lesion size did not appear to significantly influence pain (data not shown). Pain levels also did not significantly differ between sBCC and nBCC, or in regards to the number of lesions.

Lesion location proved to be a strong predictor of pain, confirming previous published findings (19). Patients with treated areas with less subcutaneous tissue and/or which were well innervated, such as the face or pretibia, experienced the greatest level of pain, requiring either irradiance adjustment or anesthesia. In comparison to prior work (authors' unpublished experience), however, where most lesions required analgesia with continuous 150 mW/cm^2 treatment, analgesics were required for only 5 of 127 lesions treated with the two-step protocol. The literature is conflicted regarding the pain reported by men vs. women in response to ALA-PDT. Grapengiesser et al. (19) described gender differences, with men experiencing higher levels compared to females. Other studies have suggested that gender along with age is a poor predictor of pain (5, 20). The results from our study, albeit limited, suggested slightly higher pain scores for females. This outcome, however, may reflect lesion location rather than a gender-based difference in pain levels. Thirteen lesions in pain-prone areas such as the face and scalp presented on female patients.

The clinical outcomes reported here for a single PDT treatment per lesion, with no limit on lesion size, compare well to most published results, showing the efficacy of ALA-PDT for sBCC's with 84% CCR at 6 month follow-up. Most partial responses represented >90% lesion clearance, with the remaining areas easily controllable with a second PDT exposure. Treatment of nBCC's was more disappointing with 36% CCR, also comparable to prior studies and likely related to the thickness of nBCC's and the difficulties associated with depth of penetration of photosensitizer along with limited penetration of the red light. The low irradiance portion of the treatment is not expected to adversely affect outcomes. In fact, low irradiance has been related to increased PDT efficacy (21) due to improved maintenance of tissue oxygenation during irradiation (10, 11, 22). Langmack et al. (23) achieved 84% CCR at 1 year in sBCC treated with ALA-PDT with only 12.6 J/cm^2 at 7 mW/cm^2, requiring 30 min of light exposure. However, only 5 of 32 lesions in that study were treated

only once. Most lesions were treated twice, and 6 needed 3 or more treatments. Since any reduction in irradiance requires additional exposure time for a given light dose, higher light doses are difficult to achieve in clinical practice because of clinical time limitations, especially in patients with numerous lesions. The approach outlined in this report facilitates the effective delivery of even high light doses with minimal prolongation of treatment time and minimal pain. Indeed from a PDT dosimetry perspective, it may be interesting to consider stepped irradiance protocols in other clinical settings where pain is not an issue. An initial low irradiance would preserve tissue oxygen and facilitate rapid photosensitizer bleaching. Because oxygen depletion results from the rate of photon absorption by the photosensitizer and not irradiance *per se*, a subsequent higher irradiance would be an efficient means of delivering increased fluence without oxygen depletion. We are aware of only one preclinical evaluation of a stepped irradiance protocol (24).

Although our PDT treatments were performed with an optical-fiber-coupled laser, a two-step irradiance protocol may be implemented easily in centers using an LED array. With the Aktilite lamp, for example, we have implemented a two-step schedule by attaching a removable, mounted sheet of neutral density film to the LED head. The initial low irradiance interval is performed with the attenuating film in place. The second, higher irradiance is accomplished by removing the film from the beam path.

In conclusion, we have validated a simple approach to minimize the pain experienced by patients undergoing topical ALA-PDT for cutaneous cancers. While this report has some limitations, i.e. uneven distribution of lesions among patients, short follow-up periods and lack of histopathological analysis, taken together with our earlier prospective study, we conclude that the protocol offers significant benefit to patients. It does not require any special equipment, reduces cost by eliminating/reducing the use of analgesics, does not unduly increase treatment time, and, importantly, permits tailoring treatments to each individual patient's needs. It thus allows delivery of larger light doses under these beneficial conditions, which represents a significant clinical improvement and may help to overcome one of the obstacles to broader clinical dissemination of this attractive therapeutic option.

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TABLE 1

Patient and Lesion Characteristics

No. patients	14
No. men	9
No. women	5
Age:	
18-25	2
26-40	1
41-60	6
61-80	5
Race: Caucasian	
No. lesions	127
Type:	
Superficial	51
Nodular	73
Bowen's Disease	3
Lesions diameter:	
1-2 cm	75
2-3cm	30
3-4cm	20
>4 cm	2
Location of lesions:	
head/neck	35
trunk	64
upper extremities	11
lower extremities	17

Table 2

Location and number of lesions scoring VAS>3 with 40 mW/cm^2 irradiance

Lesion Location	No. of Lesions with >3 VAS[1]
Chest	1
Arm	4
Back	4
Upper leg	1
Lower leg	7
Head & Neck:	
Nose	1
Philthrum	1
Malar	2
Scalp	3

[1] Lesions from 11 different patients