A Trial of Short Incubation, Broad-Area Photodynamic Therapy for Facial Actinic Keratoses and Diffuse Photodamage

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Background: There is no completely satisfactory treatment for multiple actinic keratoses (AKs).

Objective: To evaluate the efficacy of short incubation, broad-area application of δ-aminolevulinic acid followed by exposure to activating light–photodynamic therapy (δ-ALA/PDT) for treatment of AKs and background photodamage. The benefit of pretreatment with 40% urea cream to enhance penetration and the use of topical 3% lidocaine hydrochloride to decrease discomfort were also evaluated.

Methods: Eighteen patients with at least 4 nonhypertrrophic facial AKs and mild to moderate diffuse facial photodamage were enrolled in the study. For 7 days, 40% urea cream or vehicle was applied to half of the treatment area, and then δ-ALA was applied to the entire area for 1, 2, or 3 hours. Lidocaine hydrochloride (3%) or vehicle cream was also applied to the entire area 45 minutes before exposure to 10 J/cm² of blue light. Pain, phototoxic reactions, AK counts, and photodamage improvement were evaluated 1 day, 1 week, and 1 month after treatment in all patients and after 5 months in 10 patients.

Results: All patients experienced mild to moderate discomfort during treatment and moderate phototoxic effects for 1 week. At 1 and 5 months there was significant reduction in AKs in all groups and significant improvement of several photodamage parameters. Different δ-ALA application times and pretreatment with urea cream or lidocaine had no significant effect on the results.

Conclusions: This δ-ALA/PDT protocol is safe and effective for AK treatment as well as for improving photodamage. Further studies with a larger cohort, longer follow-up, and histologic confirmation of the clinical data would be of value.

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Skin cancer has been described as an epidemic in the United States with well over 800,000 new cases annually.1 Premalignant actinic keratoses (AKs) are precursors of invasive squamous cell carcinomas2 and a highly significantly associated risk factor for all forms of skin cancer.3 Actinic keratoses are extremely prevalent, affecting over 50% of fair-skinned, elderly white individuals in some countries.4 Clinically, AKs are diagnosed as persistent, easily palpable, rough or "gritty," usually erythematous patches several millimeters to perhaps a centimeter in diameter, occurring in a photodistribution, classically on the face and bald scalp of older fair-skinned individuals in the setting of moderate to severe diffuse photodamage.5 Importantly, histologic sampling reveals the same nuclear atypia and “loss of polarity” or disordered epidermal maturation in the surrounding photodamaged skin as in the clinically detectable AKs.6 Treatment of AKs is motivated by both their potential for progression to invasive squamous cell carcinoma and their cosmetic liability and/or discomfort. Patients with relatively few AKs are most often treated with local liquid nitrogen cryotherapy,7 a treatment modality associated with mild to moderate discomfort, and monitored at intervals of several months to a year for new and recurrent lesions that are then also treated.7 Patients with extensive AKs are usually offered treatment with topical fluorouracil8 or, more recently, diclofenac9,10 cancer chemotherapeutic agents applied twice daily for several weeks to broad areas in an effort to destroy “subclinical” as well as clinically apparent AKs.11 However, such treatment is invariably associated with pain, pruritus, and burning, and patient compliance is poor. Recently, regimens using the immune modifier imiquimod have been developed.12

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Photodynamic therapy (PDT) is by definition the use of a photosensitizing drug and its activating wavelength of light to achieve destruction of target tissue (or other therapeutic goal) through a photochemical reaction involving oxygen. Photodynamic therapy using the porphyrin analogue porflimer sodium (Photofrin [dihematoporphyrin]; Quadra Logic Technologies, Vancouver, British Columbia) and visible light has been used for many years on a limited basis to treat malignancies in the skin, particularly cutaneous metastases of generally incurable disease. However, the intravenous route of administration, the persistence of drug in tissues, and hence the need to scrupulously avoid light for weeks required patient hospitalization, and use of scrapping protocols restricted Photofrin/PDT to clinically detectable tumors.

In 1999, the Food and Drug Administration (FDA) approved as safe and efficacious a novel form of PDT for spot treatment of AKs. The therapy uses a topically applied 20% solution of 5-aminolevulinic acid (δ-ALA) that is absorbed and metabolized by epidermal cells to protoporphyrin IX (PpIX), a highly photosensitizing compound in the heme biosynthesis pathway. The treated area is then exposed to porphyrin-activating wavelengths of light in the Soret band (400-410 nm). The FDA-approved protocol specifies a 14- to 18-hour delay between δ-ALA application and light exposure, which was demonstrated in the pivotal studies to be sufficient for therapeutic photosensitization, and restricts application to clinically apparent AKs. As they would with cryotherapy, patients experience moderate discomfort in the treated areas during tissue destruction, followed by erythema and sometimes crusting, all resolving within 4 weeks after therapy.

Thus, in this protocol, δ-ALA/PDT clears 88% of thin AKs and 78% of moderately thick AKs after 1 treatment, but requires physician office visits on 2 consecutive days and is not superior to cryotherapy.

The aim of the present study was to evaluate the safety and efficacy of short incubation (1, 2, or 3 hours), broad-area application δ-ALA/PDT for treatment of multiple AKs and associated diffuse background photodamage. Pretreatment of the facial skin with a known penetration enhancer to reduce the required incubation time for δ-ALA and the use of a topical anesthetic to decrease the expected discomfort during PDT were also examined.

**METHODS**

**MATERIALS**

A 40% urea cream (Carmol 40; DOAK Dermatologics, Fairfield, NJ) and its vehicle base alone were supplied by the manufacturer in coded tubes labeled A and B. Lidocaine hydrochloride (3%) in a mildly acidic “acid mantle” base (LidaMantle, DOAK Dermatologics) and its vehicle base alone were similarly supplied by the manufacturer in coded tubes labeled C and D.

The 20% δ-ALA solution (Levulan Kerasticks) used in this study was supplied by DUSA Pharmaceuticals Inc, Wilmington, Mass. Each applicator tube contains 2 sealed glass ampules, one with 354 mg of δ-ALA hydrochloride powder and the other with 1.5 mL of a hydroalcoholic solvent. The vials are crushed within the applicator at the time of use, and the mixture is hand shaken for 3 minutes to dissolve the δ-ALA powder. Then it is applied through the applicator sponge tip evenly to the skin. One applicator is sufficient to treat the entire face. The fluorescent blue light source (BLU-U, DUSA Pharmaceuticals, Inc) emits a narrow spectrum of light with a peak output at 417 ± 5 nm.

**EXPERIMENTAL DESIGN**

The Western Institutional Review Board, Olympia, Wash, approved the research project. Eighteen patients (11 women and 7 men) aged 41 to 76 years and 48 to 60 years, respectively, with at least 4 nonhypertrophic AKs and mild to moderate diffuse facial photodamage, were enrolled from a general dermatology practice after giving informed consent. Photodamage severity was determined using the validated Griffiths scale (0-8). The patients’ clinical features were compared with 3 standardized photographs showing no damage (0) to severe damage (8).

Exclusion criteria included a history of porphyria or photosensitivity, hyperkeratotic AKs, active infectious disease, pregnancy or lactation, or use of photosensitizing drugs (eg, tetracycline and retinoids). All patients received δ-ALA/PDT but were randomized to receive 1 hour, 2 hours, or 3 hours of δ-ALA incubation before exposure to the blue light source. The patients were not exposed to sunlight during the incubation period and were instructed to avoid sun exposure for 48 hours after treatment. All patients were asked to pretreat half of the treatment area (left or right side randomly) with coded preparations of 40% urea cream (Carmol 40) and the other side with vehicle cream daily for 7 days (split face and double-blinded) before the scheduled PDT treatment. Lidocaine hydrochloride (3%) in a mildly acidic “acid mantle” base (LidaMantle) or the vehicle cream was applied as a coded preparation to the entire face 45 minutes before PDT in a randomized double-blinded fashion. Immediately before exposure to the PDT light source, the face was examined under Wood’s light illumination (model No. 9312; Burton Medical Products, Chatsworth, Calif) to detect the characteristic coral-red fluorescence emitted by porphyrins for comparison with the results obtained using the 14- to 18-hour δ-ALA incubation. Patients then received 16 minutes and 40 seconds (10 J/cm²) of blue light. The protocol specified that patients were to be evaluated after 1 day, 1 week, and 1 month.

All 18 patients were evaluated after 1 day and 1 week, and 17 of 18 patients were evaluated after 1 month. Ten patients were available for a subsequently requested follow-up visit at 3 months (6 from the 1-hour group and 4 from the 2-hour group). Pain, phototoxic reactions, AK counts (both total and target lesions), improvement in specific features of photodamage as assessed by the 8-point Griffiths score index, and subjective (patient)- and objective (investigator)-assessed global cosmetic improvements were evaluated. Phototoxic parameters including erythema, edema, and crusting were graded as follows: 0, none; 1, focal; 2, mild; 3, moderate; and 4, severe. Local cutaneous pain was graded as follows: 0, none; 1 to 3, mild; 4 to 6, moderate; and 7 to 9, severe. Cosmetic improvement parameters were graded as follows: 1, 90% or greater im-
provement; 2, 75% to 90% improvement; 3, 50% to 75% improvement; 4, less than 50% improvement; 5, no change; and 6, worse than baseline.

STATISTICAL ANALYSIS

Statistical analyses investigating the effect of PDT on AKs and diffuse photodamage and the effect of 3% lidocaine hydrochloride cream on PDT-associated pain and of 40% urea cream pretreatment on erythema, edema, and crusting as well as on the therapeutic effect on AKs and photodamage were performed using the general linear model (multivariate analysis) (SPSS version 10; SPSS Inc., Chicago, Ill.). We hypothesized that increased δ-ALA penetration will increase both phototoxic and therapeutic effects of PDT. However, the different groups (1-, 2-, and 3-hour incubation times and 40% urea cream and vehicle pretreatment) were combined because the analysis showed no significant effect of δ-ALA incubation time or 40% urea cream pretreatment on the tested parameters (see “Results” section) for the definitive analysis investigating the effect of short δ-ALA incubation times on AKs and photodamage. Because of the nonlinear nature of the evaluation scale, the nonparametric Friedman test (SPSS version 10) was used for definitive analysis and the effect of δ-ALA incubation time was determined separately for each parameter. Confidence intervals were examined using the Explore program (SPSS version 10).

RESULTS

Of the 18 patients, 17 completed the 1-month study and 1 discontinued for personal reasons. Ten patients were available for the 5-month follow-up visit, which was not specified in the original protocol. No patient reported adverse reactions to urea vs vehicle cream pretreatment of the face nor to the use of topical anesthetic vs vehicle cream. No patient had detectable fluorescence when measured with a Wood’s lamp immediately before the PDT light exposure, in contrast to high-fluorescence yield in both AKs and perilesional skin after 14 to 18 hours of incubation,25,28,29 which peaked at 11 ± 1 and 12 ± 1 hours, respectively.25

PAIN

Pain, in the form of stinging and burning, is expected during PDT25 and was subjectively graded on a 0-9 scale (none to severe). Lidocaine hydrochloride (3%) cream or its vehicle was applied 45 minutes prior to light exposure. In addition, patients were given a handheld fan to cool the skin during light exposure and were instructed to take acetaminophen (500-mg) tablets as needed to relieve pain in the days following treatment.

All patients noted painful sensations soon after beginning blue light exposure. No patient asked to discontinue treatment because of pain, but all acknowledged at least mild to moderate discomfort when questioned immediately after the exposure and all had used the fan for relief. Neither urea cream pretreatment nor length of δ-ALA incubation influenced the reported pain level. Pain scores were 4.4 vs 3.9 in the 1-hour 40% urea vs 1-hour vehicle groups, respectively; 3.8 vs 4.2 in the 2-hour 40% urea vs 2-hour vehicle groups, respectively; and 5.2 vs 5.8 in the 3-hour 40% urea vs 3-hour vehicle groups, respectively, demonstrating no effect of pretreatment with 40% urea vs vehicle alone on pain during PDT (P = .87). The slightly higher 3-hour pain scores did not differ statistically from the 1-hour and 2-hour scores (P = .38).

The application of 3% lidocaine hydrochloride 45 minutes before light exposure seemed modestly superior to its vehicle for pain control, with 35% of patients reporting no to mild pain (score, 0-3) compared with 14% in the vehicle group, but this did not reach statistical significance (P = .65). Of note, in this study design, patients did not have the opportunity to compare sensation in 3% lidocaine hydrochloride-treated skin with that in vehicle-treated skin, since each patient received only 1 of the 2 test products. Patients generally reported moderate posttreatment discomfort requiring analgesia with acetaminophen for up to 3 days.

Consistent with the sensation experienced on the 2 sides of the face during PDT, pretreatment with urea vs vehicle cream did not affect the pain experienced on the 2 sides of the face during PDT (P = .99). There was also no significant effect of anesthesia applied 45 minutes prior to PDT treatment on PDT-induced pain whether patients were pretreated with 40% urea or vehicle (P = .15) or whether δ-ALA was applied for longer periods (3 hours vs 1 or 2 hours; P = .14).

PHOTOTOXIC REACTIONS

Moderately severe phototoxic reactions were seen on day 1 after PDT in all patients. Findings consisted of moderate to severe erythema, mild to moderate edema, and occasional small areas of crusting (Figure 1). Neither pretreatment protocol (urea vs vehicle cream) nor length of δ-ALA incubation (1, 2, or 3 hours) affected this severity. Severe, moderate, and mild erythema was seen in 35%, 59%, and 6%, respectively, of split faces pretreated with urea cream compared with 52%, 35%, and 6%, respectively, of split faces treated with vehicle cream. Moderate, mild, or no edema developed in 47%, 47%, and 6%, respectively, of split faces treated with urea cream, while severe, moderate, and mild edema developed in 6%, 29%, and 65%, respectively, of split faces treated with vehicle control cream. Focal crusting developed in 24% of those pretreated with urea cream compared with 18% of patients pretreated with vehicle control cream. Most patients (76% of split faces treated with urea and 82% of split faces treated with vehicle) had no crusting.

These parameters were reevaluated 1 week after PDT. Generally, and as expected, patients displayed less erythema, edema, and crusting after 1 week compared with 1 day after treatment (Figure 1), and although there appeared to be a trend toward more persistent moderate edema in facial skin pretreated with urea cream compared with vehicle control (6% vs 0%), this trend was not statistically significant (P = .09). The magnitude of erythema, edema, and crusting after 1 week was also not affected by incubation time with δ-ALA (P = .95) nor by combinations of these factors (P = .17).

No patient had erythema, edema, crusting, or postinflammatory hyperpigmentation at 1 month, and there was no consistent or significant difference in appearance between the 2 sides of the face (urea vs vehicle pretreatment). One patient had a limited and self-resolving reactiva-
tion of herpes simplex infection of the upper lip, which began 5 days after PDT and resolved spontaneously. No adverse events or complications of hypopigmentation and hyperpigmentation or scarring were observed in this patient sample at 1 or 5 months of follow-up.

ACTINIC KERATOSES

By 1 month, 96%, 94%, and 85% of target AKs had cleared for the 1-, 2-, and 3-hour incubation groups, respectively, percentages that were not significantly different (P=.46). Of total AKs, 93%, 84%, and 90% reductions were noted for the 1-, 2-, and 3-hour incubation groups, respectively, percentages that were not significantly different (P=.54). At 5 months, the overall clearance rates were 87% and 94% for target AKs in the 1- and 2-hour incubation groups, respectively. For total AKs, the overall clearance noted for the 1- and 2-hour incubation times was 90% and 89%, respectively (Figure 2). No patients in the 3-hour group were seen at 5 months.

Figure 3 shows a representative patient at baseline and 5 months. There was no difference in clearing rates at either 1 month or 5 months between facial areas pretreated with urea vs vehicle. For both groups, AK numbers significantly decreased with time (P<.001). Of the 18 patients treated with δ-ALA/PDT, 11 had complete resolution of their AKs 1 month after treatment. Of the 10 patients who were available for follow-up 5 months after treatment, 7 displayed complete resolution. The confidence interval for target AKs (4) remaining was –0.1 to 0.5 at 1 month and –0.3 to 1.1 at 5 months. The confidence interval for total AKs remaining was –0.2 to 1.4 at both 1 and 5 months, encompassing the cure rates reported in the pivotal studies with 14- to 18-hour δ-ALA incubation time for treatment of discrete AKs alone.

EFFECT ON DIFFUSE PHOTODAMAGE

Photodynamic therapy modestly but significantly improved the overall Griffiths score as well as the severity of sallowness and fine wrinkling (Figure 4). Improvement in mottled hyperpigmentation was of borderline significance. In the 10 patients seen at all 3 times (base-
line, 1 month, and 5 months) after a single δ-ALA/PDT treatment, skin quality and the overall blended score of all parameters improved by a 0.5 to 1.0 grade (P < .001). Specifically, Griffiths score improved by a 0.7 grade (P < .006), fine wrinkling by a 1.2 grade (P < .002), sallowness by a 1.5 grade (P < .001), and mottled pigmentation by a 1.1 grade (P = .05). Both Griffiths photodamage score and sallowness showed additional improvement at the 5-month evaluation point compared with the 1-month visit. Statistically, the borderline significant difference in mottled pigmentation was most likely due to the large variance of this parameter at baseline, since many individual patients notably improved (Figure 3). There was no effect on coarse wrinkling. Skin quality (the overall blended score of all parameters) also improved significantly.

**Figure 3.** A patient treated with δ-aminolevulinic acid/photodynamic therapy showing multiple actinic keratoses at baseline (arrows). B, The lesions have resolved within 1 month following therapy.

**Figure 4.** δ-Aminolevulinic acid/photodynamic therapy improves diffuse photodamage. After 1 month, δ-aminolevulinic acid/photodynamic therapy significantly improved several photodamage parameters including Griffiths score, fine wrinkling, and sallowness. Both Griffiths score and sallowness showed additional improvements at 5 months. Mottled pigmentation improved as well, although the result was only of borderline significance, probably because of a large variance of this parameter at baseline. There was no effect on coarse wrinkling. Skin quality (the overall blended score of all parameters) also improved significantly. Error bars indicate SD.
and 18% (n = 3) as fair. At 1 month, investigator-determined improvements for all patients were judged as fair/average. At 5 months, 5 patients (50%) were judged as displaying good improvement and the rest maintained their fair/average improvement. Most patients commented on decreased roughness of the skin, although this was not objectively measured. Figure 5 shows representative pretreatment and posttreatment photographs. It is important to note that the 5-month data were obtained in the fall, after most patients had at least some degree of sun exposure during the summer.

COMMENT

δ-Aminolevulinic acid is a prodrug that is converted intracellularly to PpIX, a potent photosensitizer, by the heme biosynthetic pathway. Cancer cells have reduced ferrochelatase activity (the enzyme that catalyzes the last step in heme biosynthesis), leading to increased PpIX levels relative to surrounding normal cells. This contributes to preferential destruction of dysplastic cells by δ-ALA/PDT.

The blue light in this study delivers a peak output at 417 ± 5 nm, roughly corresponding to maximum PpIX light absorption, and penetrates in ample amounts to a depth of 1 to 2 mm, which is well below the epidermis that ranges in thickness between 0.1 mm (eyelid) to 1.5 mm (palms and soles). Although we were unable to detect red fluorescence in our patients’ skin after short δ-ALA incubation times, all patients experienced therapeutic phototoxic effects. The cure rates at 1 and 5 months were comparable with other studies in which longer incubation times were used and fluorescence was detected, suggesting that Wood’s lamp fluorescence is an insensitive indicator of PpIX presence.

One of the challenges of topical PDT is adequate penetration of the hydrophilic δ-ALA solution through the stratum corneum, motivating use of occlusion to enhance ALA penetration. In the present study, 40% urea cream applied daily for 1 week prior to PDT was evaluated as a penetration enhancer but proved unnecessary to achieve therapeutic PpIX levels. Whether such pre-treatment would prove useful in PDT for hypertrophic AKs was not examined in this study.

Pain during photodynamic therapy is expected, requiring interventions for pain control including application of ice, use of a fan, interruption of treatment, forced cooled air, and topical and oral analgesia. In this study, 3% lidocaine hydrochloride cream topically applied 45 minutes prior to light exposure offered minimal and statistically insignificant pain control. Because lidocaine is known to provide at least modest pain relief after topical application, the lack of significant benefit in this study probably relates to the small sample size, imprecision of the measurement, and inability of patients to compare the active vs vehicle control creams on their skin, since each patient used only one of the preparations.

The phototoxic reactions with erythema and edema seen in this study were considerable in intensity and associated with discomfort during the first 48 hours after treatment, but these reactions abated relatively rapidly in most patients, in sharp contrast to cryotherapy or topical chemotherapy with fluorouracil or imiquimod. Despite the lack of uniformity in incubation times, light sources, drug vehicles, and exposure times and fluences, published studies on PDT demonstrate considerable efficacy for AKs. In a recent large study, non-hypertrophic AKs showed a cure rate of 72% and 99% with 1 or 2 spot treatments, respectively, with a recurrence rate of 27% at 6 months. Furthermore, 88% of Bowen disease cases and 99% of superficial basal cell carcinoma cases resolved after 2 treatments, with a recurrence rate of 19% and 13%, respectively, at 6 months. In another 2 studies, 3-hour application of a methylated form of δ-ALA followed by red light exposure resolved 75% and 89% of spot-treated thin AKs at 3 months, compared with 80% of similar lesions treated with cryotherapy. In those studies, PDT was associated with better cosmetic results and higher patient satisfaction than cryotherapy.

Actinic keratoses responded very favorably to short incubation times in the present study, with clearance rates comparable with those in the pivotal trials assessing the now FDA-approved 14- to 18-hour incu-
Photodynamic therapy using topical δ-ALA for as little as 1 hour followed by blue light exposure is well tolerated and highly effective for facial AKs, with approximately 90% resolution after 1 and 5 months. In addition, broad-area δ-ALA/PDT also improves skin appearance by reducing wrinkling, sallowness, and dyspigmentation. The present study demonstrates that broad-area δ-ALA/PDT is as safe and effective for treatment of AKs as local δ-ALA/PDT and conventional cryotherapy. In addition, broad-area δ-ALA/PDT appears at least as efficacious for multiple AKs and diffuse photodamage as conventional fluorouracil therapy and is far better tolerated. Another advantage compared with existing modalities is its controlled delivery, allowing a complete and homogeneous treatment of the face and/or scalp while eliminating the need for patient compliance. Finally, because the phototoxic injury occurs intracellulary, the risk of dermal scarring is theoretically less compared with many other modalities intended to “resurface” the skin. Further studies with larger cohort, prolonged follow-up periods, and histologic confirmation of the clinical data would be valuable to the dermatology community.

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