IN-DEPTH REVIEWS

Photodynamic Therapy in 2020: Lights in the Darkness

Neal Bhatia, MD[1]

[1]Director of Clinical Dermatology, Therapeutics Clinical Research, San Diego, CA

ABSTRACT

Photodynamic therapy (PDT) is an integral treatment modality for treating the entire process of photodamage, based on what is understood about the pathogenesis of actinic keratosis and the consequences from treating only visible spots and not the underlying disease. Dermatologists must consider incorporation of treatment in combination with duration, frequency, and tolerability of local skin reactions. These considerations are important, along with the combination of topical therapies and intermittent cryotherapy of individual actinic keratoses. Aside from costs and patient demographics, adaptation by dermatologists can influence variability in long-term treatment algorithms. There are multiple published guidelines and consensus statements for the US and Europe to promote safe incorporation of both blue and red light along with the variable concentrations of ALA by dermatologists. However, there is a lack of head to head studies and comparative superiority as well as any evidence to support the use of topical agents. As management of local skin reactions becomes more commonplace, so will improved management of PDT to foster patient safety.

INTRODUCTION

As 2020 continues to be the most chaotic year in recent history, and as dermatology practices open up again, the realization that the mechanisms of skin carcinogenesis did not stop for the quarantine are beginning to show up. Dermatologists can agree that actinic keratoses (AKs) do not believe in social distancing even though they can hide behind a mask. All joking aside, now that treatment options that could create open wounds are no longer on hold, photodynamic therapy for AKs, NMSC, Acne, and other uses can be safely performed with proper management of expectations, local skin reactions, and combinations with topical treatments. To be clear to those with questions, PDT itself does not increase risks for contracting any infection, let alone from the Coronavirus, but attention to cleaning and sterilizing between treatments is essential for patient safety.

BACKGROUND + UPDATES

Fundamentals of Photodynamic Therapy

As a reminder, or for those not familiar with the mechanisms of action of photodynamic therapy (PDT), the three essential components are: 1) A photosensitizer concentrated in target tissue, which in the US market is aminolevulinic acid (ALA) delivered 10% in gel or 20% in stick

preparations; 2) A light source of variable wavelength and energy (BF-RhodoLED® is an LED lamp emitting red light at a wavelength of 635 nm, BLU-U wavelength occurs at 417 ±5 nm); and 3) Oxygen available for conversion into Reactive Oxygen Species.[1] Of note, the duration of action of the free oxygen radicals is about 40 nanoseconds, but, once the impact on tissue is made, the key for successful treatment involves optimal time and temperature.

That said, other light sources are being regularly studied. Evidence supporting the use of low fluence illumination compatible with activation spectra of porphyrins led to a pilot study in Israel involving 15 patients ages 45-74. In the trial, one treatment using 20% ALA cream under occlusion for 3-4 hours followed by 45 minutes exposure with red LED traffic lamp 625 nm bulbs led to a tolerable treatment with minimal pain. Moreover, only 2 of 15 patients needed two treatments with no recurrences reported after 3 months. However, the verdict is still out on efficacy for sBCC and SCC *in situ* and other indications.

Once the mechanisms are understood and the equipment is in place, the right patient has to be screened and educated about the role of therapy and potential outcomes. The staff needs to review any oral medications as well as any topical prescription or non-prescription products on the patient's face or scalp. In addition, the medical status of patient, the size, location, number and duration of AKs/tumors, as well as the evolution of the growth pattern, are all essential historical considerations. In addition, timing is critical with treatments, as the patient must not have any upcoming social events, photo sessions, or vacations. The patient must also be committed to staying indoors and out of the sun for the necessary amount of time to protect against exuberant responses. Furthermore, make sure that the procedure is not scheduled on the same day as a flight, a golf outing, a wedding, or anything else except hibernation.

The staff and the office have to be just as prepared. There needs to be adequate training on the procedure's dynamics, as well as making sure enough treatment time is allotted on everyone's schedule to manage pre and post-treatment expectations and provide sufficient counseling. Incorporation of all available methods for pain control is a must. Fans, mist sprays, cool packs, and a hand to hold are important for the first few minutes for treatment. There is a solid rationale for microneedling prior to treatment despite the lack of reimbursement or a coding algorithm. In a randomized, single-blinded, split-face controlled trial, 32 patients were treated either with a 10-min or 20-min incubation using ALA-BLU PDT after pretreatment with either a microneedle (200 um) or sham roller; which was blinded to laterality in an attempt to measure AK resolution and assess pain associated with microneedle pretreatment.[3] The group treated with 20-minute incubation experienced AK clearance of 76% vs 58% on the sham side ($P < .01$) The pain assessment was not significantly different between the microneedle and sham sides (0.7 and 0.4; $P = 0.28$), respectively. The authors concluded that PDT with microneedle pretreatment at a 20-minute ALA incubation time significantly improved AK clearance and the procedure was virtually painless, but a 10-minute ALA incubation time did not reach significantly different AK clearance.[3]

Time and Temperature

The labelled indication for 20% ALA with blue light calls for an incubation of 14 hours, meaning treat the day before and stay

indoors to avoid activating the light.[4] Ironically, these treatments were indicative of how daylight PDT was conducted, given that the patients who had ALA applied the day before would immediately start reacting once they went outdoors to come back to the clinic for the light treatment.

In reality, despite the multitude of published variations of incubation times that have been accepted as options, there is data exploring the logarithmic conversion of ALA as measured in an actinic keratosis papule. In a study of 20 patients examining surface PpIX, measurements were taken using a hand-held fiber optic–based fluorescence dosimeter. Examination of the fluorokinetics was measured at 60% at one hour but 100% at two hours.[5] Although the correlation was not compared with clinical efficacy of treatment, it does suggest the potential for issues with absorption and possibly makes a case for longer incubation times for improved clearance. On the other hand, a recently published study examined the concept of "simultaneous PDT." In this bilaterally controlled, intrapatient study of 23 patients, 20% ALA was applied to the entire face and/or scalp. On one side blue light was started immediately and continued for either 30, 45, or 60 minutes while on the contralateral side, blue light began 1 hour after ALA application and lasted 1000 sec ("conventional PDT"). Pain was evaluated on a 0-10 scale and AK counts were determined by clinical exam and photography. All patients experienced significantly less pain during simultaneous illumination than during conventional PDT 3 months post-treatment, and clearance was nearly identical on the two sides (non-inferiority ± 15% margin). The conclusions suggested that the “simultaneous PDT” regimen is essentially painless with efficacy similar to conventional PDT.[6] Although the study was relatively small, and additional studies were recommended, the practical aspects of having bulbs illuminated for extended periods could prove financially prohibitive.

Coding Updates for 2020

The CPT Codes for photodynamic therapy have been updated to reflect the definition of the procedure: Photodynamic therapy by external application of light to destroy premalignant and/or malignant lesions of the skin and adjacent lip mucosa by activation of photosensitive drug(s), each phototherapy exposure session. The previous code in use was 96567, which should now be used only when a physician does not directly participate in the PDT treatment delivery. Dermatologists should now use the two codes 96573 and 96574. The 96573 code is to be utilized when the physician or other practicing clinician applies the photosensitizer and initiates the light illumination, while 96574 is used when curettage or debridement of the individual actinic keratoses is performed with the procedure.[7]

The code means applying the ALA and turning on the light but not necessarily staying in the room the entire time with the patient; however, remaining present is good practice to improve the patient’s outcomes, as talkesthesia and hand-holding can make the experience better and ensure that a second treatment in the cycle can be considered.

Daylight PDT: Realistic Options

In Europe the concept of using daylight as the light source with methyl-aminolevulinic acid was studied using multiple parameters. The first major study published in 2008 compared the efficacy and tolerability of daylight PDT to red light PDT both using MAL, based on the continuous and sustained activation of protoporphyrin IX by

daylight as compared to the concentrated activation by red light. In this trial, 29 patients with AKs on the head were treated with MAL-PDT then divided into one area illuminated by red LED light (37 J cm(-2)) after 3-h incubation with MAL under occlusion, compared to the other side where MAL cream was applied under occlusion for 30 minutes then treated in the daylight for 2.5 hours. The investigators reported no significant difference in efficacy between the two treatments (P = 0.13), (79% in the daylight area vs 71% in the LED area), but there was more pain reported on the side with illumination using LED than daylight (P < 0.0001). Local skin reactions were similar on both sides. The observations made about shorter incubation time in the office and the efficacy demonstrated by continuous activation of porphyrins by daylight offered convenience and tolerability.[8] Since then, many studies have evaluated daylight PDT using variations in concentrations of MAL,[9] exposure times,[10] and impact of AK thickness,[11] all of which led to the conclusions of high tolerability with comparable efficacy to conventional treatments. Of note, these treatments were performed under any time of day or condition except when it rained. The patients were to use a sunscreen of SPF 20, treated with curettage and application of MAL followed by daylight exposure within 30 minutes. After 2 hours of daylight the MAL cream was removed and the patients remained outdoors for the remainder of the day.[10,11]

The risks of recurrences with daylight PDT were evaluated in a study in 2019 comparing a nanoemulsion gel containing 7.8% 5-aminolaevulinic acid to 16% MAL cream. There were 52 patients who underwent one daylight PDT session with either photosensitizer and followed for both 12 weeks and one year. After 12 weeks from one treatment, almost 80% of the AKs treated with BF-200 ALA gel and 76.5% of the lesions treated with MAL cream were completely cleared. However, the recurrence rates 1 year after treatment were 19.9% for the BF-200 ALA arm compared to 31.6% for patients treated with MAL.[12]

A small pilot study using daylight PDT for actinic cheilitis was performed in Israel with 11 patients (3 females, 8 males) with mean age of 59. Each patient underwent a biopsy to confirm the diagnosis and exclude the presence of SCC, which was repeated at the end of the study.

The protocol mandated 2-3 treatments with each patient applying sunscreens, followed by curettage of lip AKs and application of a thick layer of MAL cream without occlusion. The patients were then exposed to 2-3 hours of sunlight between 8-11 am and then remained indoors. The investigators reported a response rate of 91% while patients reported mild erythema and minimal to no pain during treatment along with improved cosmetic outcomes.[13]

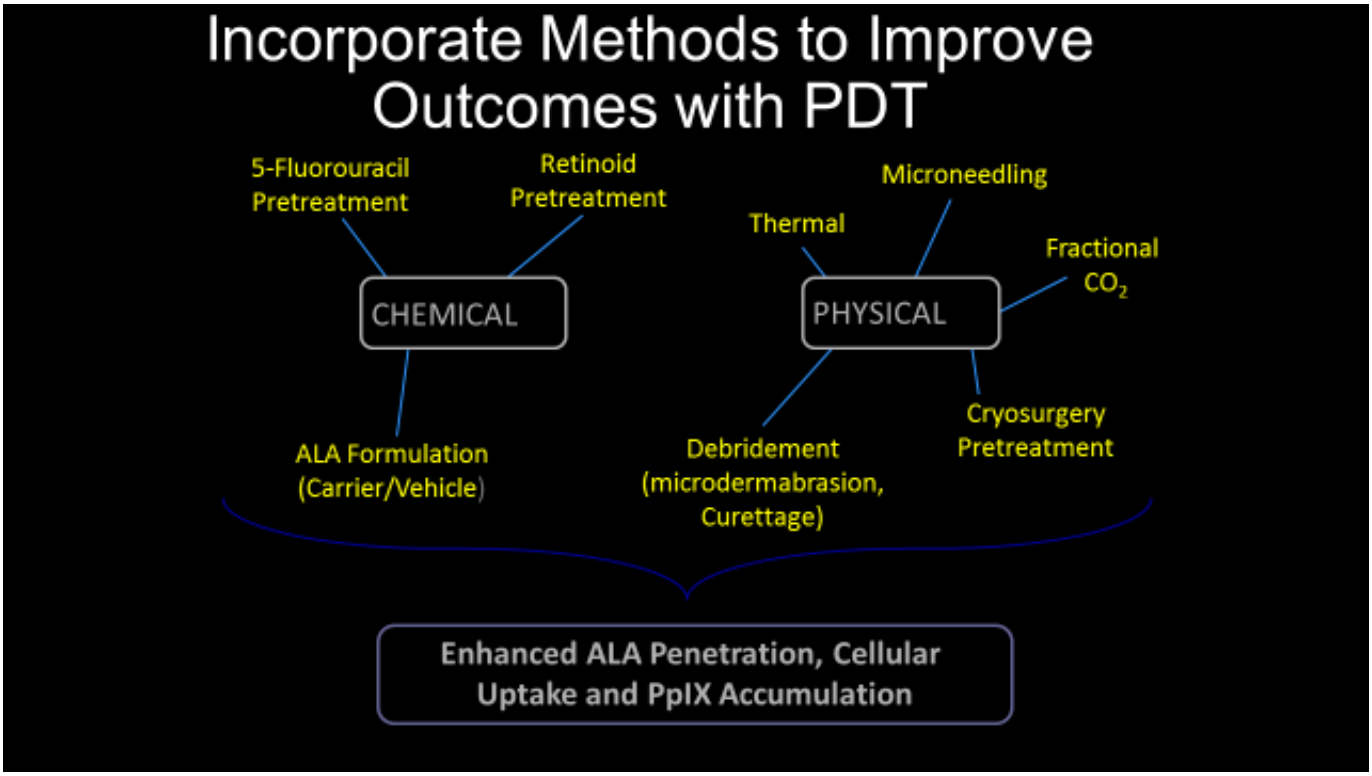
Ironically, as the labelled indication for 20% ALA/Blue light calls for a 14 hour incubation,[4] this is actually a modified version of daylight PDT since the patients were treated the day before and were exposed to the morning sun the following day. Following what we know about PDT, the resumed reactions were probably somewhat painful, although that data does not exist. The low pain potential and convenience of daylight PDT are compelling but unlike practices in countries with socialized medicine, the inherent obstacles for treatment with daylight PDT are multiple…the most glaring being the lack of predictable local skin reactions with this off-label method of PDT, as standardization of an algorithm continues to be developed.

Aside from the obvious counter arguments to the use of daylight PDT in the US market, the lack of a CPT code that supports reimbursement of this procedure and the risk of financial obligation for the photosensitizing agent make incorporation into regular private practice difficult. Conversely, an opportunity exists to offer the procedure to patients who pay out of pocket or have high deductibles that also want to avoid the pain of the treatment, as long as there is appropriate monitoring of skin reactions and proper consent is obtained.

treatment on one side of the body, either the face, scalp, forearms, with topical 5% 5-FU cream as pretreatment for 6 days, with no pretreatment on the other side.

Both sides were incubated for 3 hours with MAL 16% cream and protoporphyrin IX (PpIX) levels were measured by noninvasive fluorimetry and skin biopsy. After red light illumination, lesion clearance was assessed at 3, 6, 9, and 12 months after PDT with red light. The study showed that PpIX levels were increased 2- to 3-fold in 5-FU pretreated

Table 1. Methods to Improve Outcomes with PDT



Optimizing Combinations

Many options for using topical therapies for actinic keratoses have been published and adapted into practice (Table 1), primarily to reduce the risks of progression to SCC as well as to possibly serve as chemoprevention with the procedure.[14,15] One study involving 17 patients involved

AKs versus the control sides with relative clearance rates after PDT 75% versus 45% without 5FU pretreatment. The mechanisms of AK clearance were thought to be the enhanced photosensitizer accumulation and p53 induction from 5- FU, and in a combined regimen could be easily integrated to reduce the recurrence of AKs and potentially reduce

the risk of SCC.[15] Similar pilot studies have been performed with imiquimod 5% cream between cycles as well as with cryotherapy, opening the door for options for dermatologists to treat the entire process.[14]

Modifications during the pandemic

The conditions surrounding the pandemic from Coronavirus lead to concerns about exposures of the same equipment to patients. After consultations with the manufacturers of the light devices, their recommendations are as follows (Table 2, Table 3):

Table 2. Blue Light:

WARNING: Turn power off and disconnect the power cord before cleaning the machine.

CAUTION: Never immerse machine in liquids. Do not use abrasive materials to clean the machine. Do not allow water to enter this device. Do not clean the inside of this device. The exterior surface of the BLU-U® may be wiped down with a mild disinfectant or isopropyl alcohol. Dry with a clean dry cloth.

The outside surface of the plastic shield may be wiped down with a mild disinfectant or isopropyl alcohol. Dry with a clean dry cloth.

If goggles are used for eye protection, their surface may be wiped down with a mild disinfectant or isopropyl alcohol after each use.

Currently, 62% or higher isopropyl alcohol is sufficient to kill COVID-19.

-- Courtesy of Lindsay Habeeb, MD Medical Affairs, Associate Director SunPharma;

Per Cleaning instructions from the BLU-U user manual (page 21):

Cleaning/Disinfecting

Table 3. Red Light:

Place replaceable plastic wrap around the user interface on RhodoLED; staff should use gloves anytime touching, adjusting, or moving the device.

Clinic staff should use more conservative PPE protective measures (i.e., face shield) when applying ALA gel to patient's face, always use gloves to apply ALA (as they should have been doing all along)

Use occlusion on face (per Ameluz label) so the patient can incubate with photosensitizer and keep office staff safe with patient keeping mask on while incubating; the occlusion serves as barrier to keep mask from touching the ALA (and occlusion prevents risk of mask redistributing ALA to mucous membranes)

Re: LSRs post PDT, recommend to patients to stay indoors out of light per label and clean hands before & after applying any sunscreens or post-PDT occlusives to speed up recovery.

-- Courtesy of Jon Lyons, PhD, MBA Director, Medical Affairs – I.S. Biofrontera, Inc. Communications regarding Ameluz/Rhodo-LED

CONCLUSION

The versatility of photodynamic therapy using various light sources, photosensitizers in different concentrations and vehicles, and in combination with various strategies will provide many options for dermatology patients with AKs, NMSC, Acne vulgaris, and other conditions. In addition, the potential for incorporation of daylight PDT into practice can open doors for patients who were once reluctant to treatment, thereby reducing skin cancer risks. Important anecdotal pearls include not shortchanging incubation times for convenience, especially for treating the extremities, optimizing every adjunct for pain control except steroids, including even a little alprazolam to reduce anxiety. Many experts would agree that PDT is probably one of the best chemoprevention strategies in addition to being an effective field treatment. As you can see, PDT has a bright future regardless of which light is turned on.

Conflict of Interest Disclosures: Dr. Bhatia is an advisor, consultant, and investigator for Biofrontera US and SunPharma

Funding: None

Corresponding Author:
Neal Bhatia, MD
Director, Clinical Dermatology
Therapeutics Clinical Research
9025 Balboa Avenue, Suite 105
San Diego, CA 92123
Phone: 858-571-6800
Fax: 858-571-6801
Email: bhatiaharbor@gmail.com

References:

1. Gold, M, "*Photodynamic Therapy in Dermatology*," New York: Springer Science, 2011
2. Enk, CD. Levi A, "Low-irradiance red LED traffic lamps as light source in PDT for actinic keratoses," *Photodermatology, Photoimmunology and Photomedicine,* Dec 2012, Vol 28, Issue 6 Pages 332-334
3. Petukhova TA, Hassoun LA, Foolad N, Barath M, Sivamani RK, "Effect of Expedited Microneedle-Assisted Photodynamic Therapy for Field Treatment of Actinic Keratoses: A Randomized Clinical Trial.," *JAMA Dermatol*. 2017;153(7):637–643. doi:10.1001/jamadermatol.2017.0849
4. Physician's Insert, Levulan Kerastick®
5. Warren C. *et al*. "Noninvasive fluorescence monitoring of protoporphyrin IX production and clinical outcomes in actinic keratoses following short-contact application of 5-aminolevulinate," Journal *of Biomedical optics*. 2010; 9/10 15(5)
6. Kaw U, Ilyas M, Bullock T, Rittwage L, Riha M, Vidimos A, Hu B, Warren CB, Maytin EV, "A regimen to minimize pain during blue light photodynamic therapy of actinic keratoses: Bilaterally controlled, randomized trial of simultaneous versus conventional illumination," *J Am Amer Dermatol* (2019), doi: https://doi.org/10.1016/j.jaad.2019.09.010
7. https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=128&ncdver=3&CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=All&KeyWord=Photodynamic+Therapy&KeyWordLookUp=Title&KeyWordSearchType=And&bc=gAAAABAAAEAAAA%3D%3D&
8. Wiegell SR, Haedersdal M, Philipsen PA, *et al*: "Continuous activation of PpIX by daylight is as effective as and less painful than conventional photodynamic therapy for actinic keratoses; a randomized, controlled, single-blinded study," *Br J Dermatol* 2008; 158:740-746.
9. Wiegell SR, Haedersdal M, Eriksen P, Wulf HC, "Photodynamic therapy of actinic keratoses with 8% and 16% methyl aminolaevulinate and home-based daylight exposure: a double-blinded randomized clinical trial," *Br J Dermatol*. 2009; 160(6):1308-1314.
10. Wiegell SR, Fabricius S, Stender IM, *et al*, "A randomized, multicentre study of directed daylight exposure times of 1½ vs. 2½ h in daylight-mediated photodynamic therapy with methyl aminolaevulinate in patients with multiple thin actinic keratoses of the face and scalp," *Br J Dermatol* 2011;164:1083-1090.
11. Wiegell SR, Fabricius S, Gniadecka M, *et al.* "Daylight-mediated photodynamic therapy of moderate to thick actinic keratoses of the face and scalp: a randomized multicentre study. *Br J Dermatol*. 2012; 166(6):1327-1332.

12. Dirschka T, Ekanayake-Bohlig S, Dominicus R, *et al*, “A randomized, intraindividual, non-inferiority, Phase III study comparing daylight photodynamic therapy with BF-200 ALA gel and MAL cream for the treatment of actinic keratosis,” *J Eur Acad Dermatol Venereol.* 2019;33(2):288-297..
13. Levi, A *et al,* “Daylight photodynamic therapy for the treatment of actinic cheilitis,” *Photodermatology, Photoimmunology & Photomedicine, January 201,* Volume35, Issue1
14. Serra-Guillen C, Nagore E, Hueso L, *et al*, “A randomized comparative study of tolerance and satisfaction in the treatment of actinic keratosis of the face and scalp between 5% imiquimod cream and photodynamic therapy with methyl aminolaevulinate, “*Br J Dermatol.* 2011; 164(2):429-433.
15. Maytin EV, Anand S, Riha M, *et al.* “5-Fluorouracil Enhances Protoporphyrin IX Accumulation and Lesion Clearance during Photodynamic Therapy of Actinic Keratoses: A Mechanism-Based Clinical Trial,” *Clin Cancer Res*, 2018; 24(13):3026-3035. Table 2 Courtesy Lindsay Habeeb, MD Medical Affairs, Associate Director SunPharma Per Cleaning instructions from the BLU-U user manual (page 21): Cleaning/Disinfecting Table 3 Courtesy Jon Lyons, PhD MBA Director, Medical Affairs - U.S. Biofrontera, Inc. Communications regarding Ameluz/Rhodo-LED