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Photodynamic Therapy Effectively Treats Actinic Keratoses Without Pre-Illumination Incubation Time

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Abstract

BACKGROUND: Actinic keratoses (AKs) are dysplastic lesions of the epidermis that have the potential to progress to non-melanoma skin cancers (NMSC). Traditional photodynamic therapy (PDT) requires a preillumination incubation time, which adds to overall in-office time and has been linked to pain. Our group has found a novel protocol to effectively treat AKs with PDT that eliminates the pre-illumination incubation period and uses 2 back-to-back cycles of 16 minute 40 seconds.

METHODS: The patient was prepped with soapy water and isopropyl alcohol, and thick AKs were descaled with a curette. Next, 5-aminolevulinic acid (ALA) was applied to the treatment areas and the patient was immediately placed under the blue light for 33 minutes and 20 seconds (two cycles of 16m/40s).

RESULTS: During therapy, the patient reported no pain. At one week, treated areas revealed a good reaction. The procedure was repeated at one month to treat residual AKs. At a 4-month follow-up, the patient's face and scalp showed near clearance of any AKs.

CONCLUSION: During PDT, the photosensitizer aminolevulinic acid (ALA), or in Europe methyl aminolevulinate (MAL), is utilized as a synthetic precursor that preferentially accumulates in dysplastic cells. The precursor then converts to PpIX via the heme pathway and causes apoptosis of the cells when excited, most commonly by either blue-violet (400–430 nm) or red (630–635 nm) light. Shorter incubation times are associated with reduced pain because less PpIX will have accumulated in the treated tissue by the start of the exposure to the light. The doubling of the light exposure time allows comparable levels of the photosensitizing molecule to accumulate and be activated so as to produce an equivalent reaction. The associated reduction in pain along with a more convenient treatment schedule makes this PDT protocol more tolerable and convenient to some patients.

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DISCLOSURES

The authors have declared no conflicts of interest.

INTRODUCTION

Actinic keratoses (AKs) are dysplastic premalignant lesions of the epidermis that often occur in Fitzpatrick I-III skin-type patients who have been chronically exposed to sunlight. If left untreated, AKs can progress to skin cancer.[1] It has been shown that the risk of progression to primary squamous cell carcinoma (SCC) is 0.6 percent by 1 year and 2.57 percent by year 4.[2] Moreover, it is accepted that up to 65 percent of all SCCs were at one time diagnosed as AKs.[2] Appropriately, early treatment and eradication of AKs is important to prevent progression to invasive disease. Treatment options for AKs vary depending on the extent of disease. Liquid nitrogen destruction is an excellent treatment for local disease, while more extensive disease requires field therapy with either photodynamic therapy (PDT), topical chemotherapy, or laser treatment.[3–13] When compared to topical chemotherapy, PDT is arguably better tolerated and offers patients less down time and pain. PDT has been approved for the treatment of mild to moderate AKs of the face and scalp, and uses a topical photosensitizer, either methyl aminolevulinate (MAL), or its ester, aminiolevulinic acid HCL (ALA), that is activated by blue or red light. Current standard of care involves the application of a photosensitizer, a preillumination incubation time of 1–3 hours, and exposure to blue-violet light (400–430 nm) for 16 minutes and 40 seconds or to red light (630–635 nm).[14,15] The photosensitizer is taken up by all cells but is particularly metabolized in pre-malignant cells via the heme biosynthesis pathway to protoporphyrin IX (PpIX) due to a relative decrease activity of ferochelatase within dysplastic cells.[15,23,24] Following blue-violet or red light exposure to these areas in the presence of oxygen, cytotoxic free radicals form and eradicate the dysplastic cells with minimal damage to surrounding tissue.[15,21,22,25,26]To date, patient enthusiasm for PDT has been limited due to the lengthy in-office procedure protocols and associated pain.[15–17] Pain is thought to be directly proportional to the length of pre-illumination incubation time as more photosensitizer is allowed to accumulate prior to the light exposure. Recent groups have sought to decrease incubation times to shorten office visits and reduce associated pain, while maintaining comparable treatment outcomes.[18–21] The shortest effective incubation time studied to date has been 1 hour by Pariser and colleagues.[21] In their study they demonstrated that shortening the incubation time correlated with decreased pain and discomfort, while maintaining efficacious results. Through our clinical experience with PDT, we have found that we can effectively treat AKs with a protocol that fully eliminates the pre-illumination incubation period and uses 2 back-to-back cycles of 16 minute and 40 seconds (33m/20s). The advantage of this approach is that it shortens overall treatment time and is associated with less pain.

CLINCAL COURSE

AW is a 56-year-old Caucasian man, with cognitive impairment and Fitzpatrick skin type II, who presented to our clinic for PDT to treat extensive actinic damage due to years of sun exposure. He had a history of basal cell carcinoma on the nasal tip treated by Mohs micrographic surgery. He subsequently sought care at our clinic to treat actinic keratoses on his face and scalp. On physical examination, the patient had erythematous scaly papules and thin plaques on his forehead, cheeks, temples and scalp, consistent with AKs. The patient also suffered from dementia, and thus was unable to tolerate complex or overly painful

treatment options. Cryotherapy had been used in the past, however given the extent of his disease, a treatment that offered greater field effect was deemed more appropriate. Initially, we attempted to use PDT with the standard 1-hour incubation time followed by the 16m/40s blue light exposure. However, the patient could not tolerate the full illumination period due to pain and the treatment was prematurely terminated. Thus, we decided to administer PDT with zero interval after ALA incubation and the start of two 16m/40s cycles of blue light (33 and 20 seconds minutes total). On the day of the procedure, appropriate patient consent was obtained and standardized photographs prior to the procedure were taken and stored on a HIPAA compliant cloud based image storage system (Figures 1 and 2). Pre-treatment prep consisted of scrubbing the face and scalp with warm soapy water and descaling hypertrophic AKs with a 4 mm non-disposable curette. ALA was then applied to the patient's face and scalp just before placing him under the blue light for 33 minutes and 20 seconds (two cycles of 16m/40s). After the light exposure, a physical sunscreen was applied and the patient was discharged home with instructions to avoid sun exposure for 48 hours. With this protocol, the patient tolerated the complete course of treatment and reported no pain (0 out of 10). At one week, the treated areas revealed resolving erythema and desquamation, indicating a good response to therapy. Despite significant improvement, the procedure was repeated at one month to further treat any residual or new actinic keratoses. Again, he tolerated the procedure well and denied any associated pain, and at one-week follow up, he showed a good reaction to treatment. Finally, at a 4-month follow-up, his face and scalp showed near clearance of all actinic keratoses (Figures 3 and 4).

DISCUSSION

Conventional PDT is approved for the treatment of mild to moderate actinic keratoses of the face and scalp and utilizes a topical photosensitizer solution that is activated by either red or blue light. Historically, PDT treatment involved the application of either ALA or MAL with a pre-illumination incubation time of 14–18 hours followed by light exposure for 16m/40s of blue or red light.[14,15] Extensive photosensitizer incubation time had been thought necessary for sufficient ALA/MAL uptake and PpIX accumulation within tissue to achieve cytotoxicity. Recently, several studies have reported comparable treatment outcomes in patients treated with shorter incubation times of 1–3 hours and one cycle of 16m/40s light exposure.[18–21] Notably, Pariser and colleagues utilized PDT with only 1 hour of incubation time and demonstrated that shortening the incubation time yields efficacious results while decreasing patient discomfort.[21]As mentioned, our patient was unable to tolerate a lengthy incubation period or the pain associated with traditional PDT. However, we were able to achieve effective clinical outcomes despite eliminating the incubation period by doubling the illumination time. In our method, sufficient PpIX accumulates and becomes activated within dysplastic cells during the 33m/20s of illumination. This may suggest the length of blue light exposure as the rate-limiting step of the cytotoxic reaction rather than ALA incubation. Importantly, decreasing incubation time limited patient discomfort. This is likely due to decreased absolute concentrations and activation of PpIX in the cells at any given time. We posit that decreased pain along with a more convenient treatment schedule will make this PDT methodology more appropriate for some patients. Of note, our patient did require a second treatment to achieve adequate results. While the benefits from decreasing the

incubation were clear, future patients undergoing this method may need to undergo more than one treatment to achieve AK resolution. In this case, due to the absence of pain or discomfort, our patient was happy to return for another round of therapy.

CONCLUSION

Blue light PDT with no incubation time and increased blue light exposure is a novel and practical new approach to a well-known treatment for actinic keratoses. It allows for the treatment of extensive AKs and minimizes pain associated with the procedure. In this clinical case, 33m/20s of blue light exposure after no ALA incubation time yielded excellent clinical effects and improved tolerability. This protocol has the potential to increase patient satisfaction and ultimately patient compliance. Further studies, particularly randomized controlled clinical trials, are necessary to substantiate and support our clinical experience.

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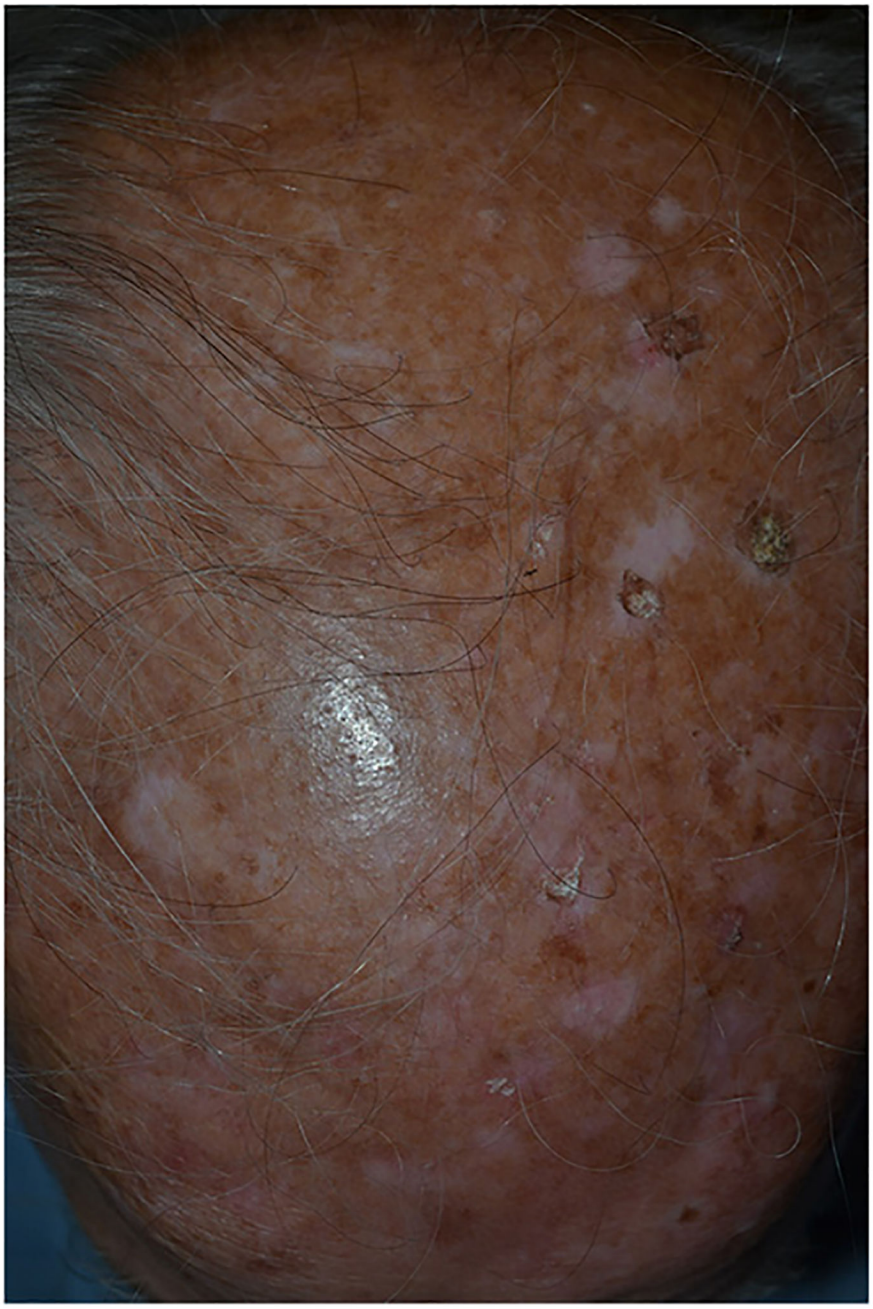

FIGURE 1.
Pre-PDT photo of AW (Scalp).

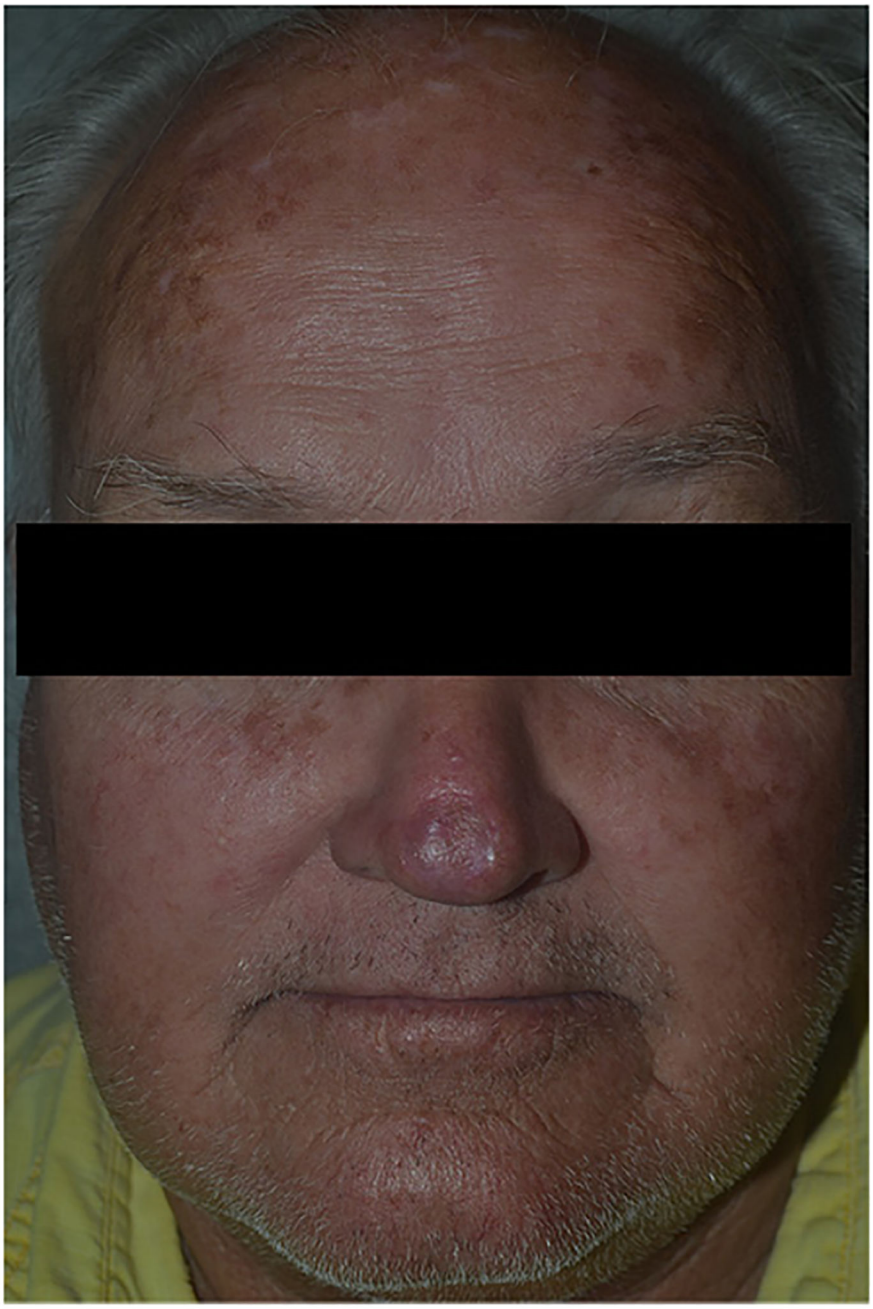

FIGURE 2.
Pre-PDT photo of AW (Face).

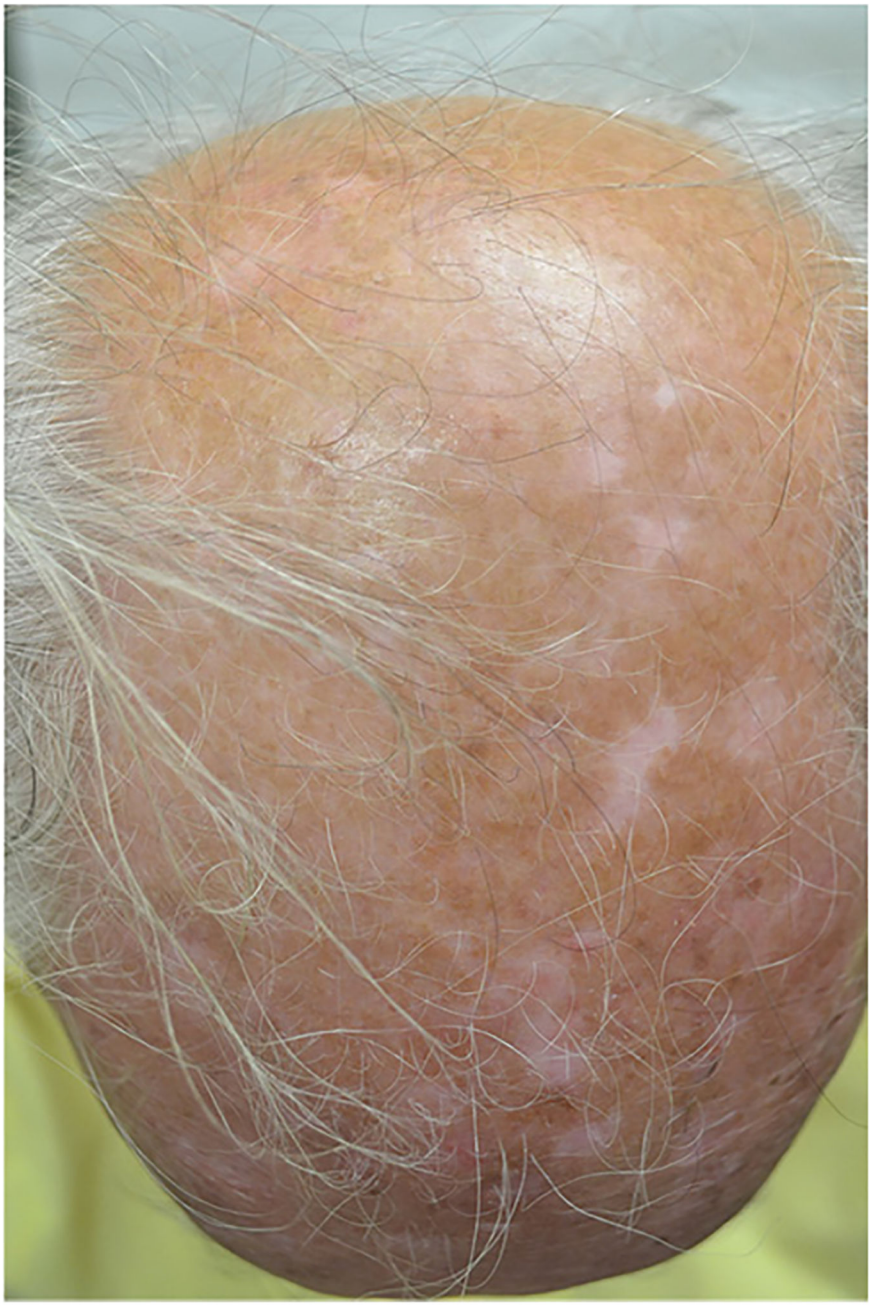

FIGURE 3.
Post-PDT photo of AW (Scalp).

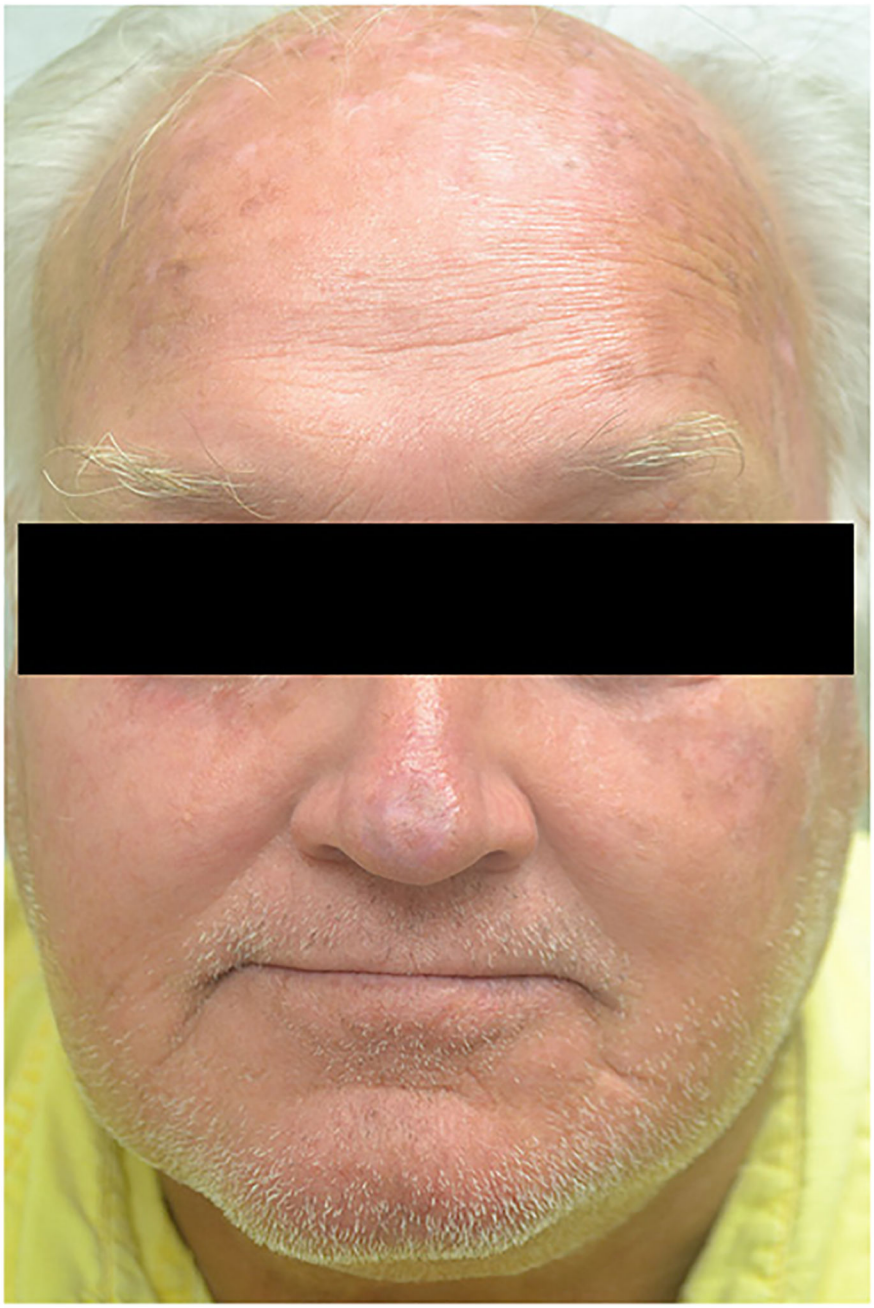

FIGURE 4.
Post-PDT photo of AW (Face).