Sustained resolution of nonmelanoma skin cancer with photodynamic therapy using 10% 5-aminolevulinic acid hydrochloride gel: A retrospective case series

Angela Moore, MD,[a,b,c,d,e] Kara Hurley, BSA,[e] Stephen Moore,[a,b] and Luke Moore[a,b]

Key words: clinical research; general dermatology; medical dermatology; nonmelanoma skin cancer; photodynamic therapy.

INTRODUCTION

Treatment options for nonmelanoma skin cancer (NMSC) such as basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and SCC in situ (SCCIS) include excision, Mohs, curettage and electrodessication, topical treatments, and radiation therapy. Some patients with NMSC refuse surgical intervention or are poor surgical candidates. Topical agents, which are often complicated by poor compliance, can have limited effectiveness, especially in SCC.

Photodynamic therapy (PDT) is a noninvasive treatment used for actinic keratoses (AKs) that involves application of a photosensitizing agent followed by illumination with a light source to activate the photosensitizing agent. The photosynthesizing agents used in PDT are derivatives of porphyrins, which are large, conjugated molecules capable of efficiently absorbing visible wavelengths of light. Common photosensitizers used for AKs include the prodrugs 5-aminolevulinic acid (ALA) and methyl aminolevulinate (MAL). After uptake of ALA or MAL by AKs, with subsequent conversion of the photosensitizer to protoporphyrin IX (PpIX), illumination activates PpIX, causes aerobic formation of reactive oxygen species, and ultimately results in apoptosis and necrosis. PpIX has maximum absorption at the blue light region while red light provides maximal tissue penetration.[1,2]

Abbreviations used:

ALA:	5-aminolevulinic acid
BCC:	basal cell carcinoma
MAL:	methyl aminolevulinate
NMSC:	nonmelanoma skin cancer
PDT:	photodynamic therapy
PpIX:	protoporphyrin IX
SCC:	squamous cell carcinoma
SCCIS:	SCC in situ

PDT with photosensitization using 10% ALA gel was approved by the Food and Drug Administration in 1999 for the treatment of AK in field-directed treatment areas measuring 20 cm^2 or smaller.[3] A meta-analysis of 25 studies investigating 10 treatment modalities for AKs showed PDT with ALA to be the most effective treatment based on clearance 12 weeks after treatment.[4] The use of PDT in NMSC has been documented in the literature.[5] To our knowledge, sparse data exist regarding recurrence of the NMSC. This retrospective case series demonstrates sustained eradication of 10 NMSC lesions using blue light PDT with 10% ALA gel with no evidence of recurrence after 5 years.

From the Arlington Center for Dermatology, Arlington, Texas[a]; Arlington Research Center, Arlington, Texas[b]; Department of Dermatology, Baylor University Medical Center, Dallas, Texas[c]; Department of Medical Education, Texas Christian University School of Medicine, Fort Worth, Texas[d]; and Department of Medical Education, Texas College of Osteopathic Medicine, University of North Texas Health Science Center, Fort Worth, Texas.[e]

Funding sources: None.

IRB approval status: Not applicable.

Consent for the publication of all patient photographs and medical information was provided by the authors at the time of article submission to the journal stating that patient gave consent for their photographs and medical information to be published in print and online and with the understanding that this information may be publicly available.

Correspondence to: Angela Moore, MD, Arlington Center for Dermatology, 711 E Lamar St, Arlington, TX 76011. E-mail: acdermacderm@gmail.com.

JAAD Case Reports 2023;38:148-51.

2352-5126

https://doi.org/10.1016/j.jdcr.2023.06.027

Table I. Patient demographics and clinical data

Case	Age	Sex	Pathology-confirmed diagnosis	Location	Thickness (mm)	Failed treatments	Incubation time (min)	Number of treatments
1	74	M	SCCIS	Right cheek	-	none	90, 90	2
2	70	M	SCCIS	Left ear	-	imiquimod 3.75% cream	60, 60	2
3	76	M	SCCIS	Right neck	-	none	90	1
4	69	M	SCC	Left ear	6	none	90, 90	2
5	87	F	SCC	Left upper chest	9	none	90, 90	2
6	70	M	SCC	R cheek	4	none	60, 60	2
7	76	M	SCC	Right crown	0.8	none	90, 90	2
8	71	F	sBCC	Right jaw	-	none	60, 60	2
9	78	M	nBCC	Right ear	4	none	90	1
10	74	M	nBCC	Nose	3	imiquimod 3.75% cream	60, 90, 60, 60	4

CASE SERIES

We identified 10 patients in the months of April and May of 2018 who were treated with PDT for NMSC of the face, scalp, neck, and chest and had 5-years follow-up data as of February 2023. All patients who met this criterion were included. Of the 10 patients, 8 were male and 2 were female. Ages ranged from 69- to 87-years-old (M = 75, SD = 5.3). Lesions consisted of 2 nodular BCCs (nBCC), 1 superficial BCC (sBCC), 4 well-differentiated SCCs, and 3 SCCISs. Two patients were treated prior with imiquimod 3.75% cream, which failed to decrease the diameter and nodularity of the lesions. Patient demographics are represented in Table I.

NMSC lesions were degreased with acetone in all patients and then debridement was performed prior to application of 10% ALA gel. The skin cancer lesions were incubated with 10% ALA gel for 60 to 90 minutes with plastic wrap occlusion (Table I). Patients were instructed to stay within the building but could walk around inside the covered atrium or office building during their incubation period. Illumination was performed with 10 J/cm^2 blue light (417 nm blue light for a duration of 16 minutes and 40 s) (DUSA Pharmaceuticals, Inc). Immediately after treatment, patients were instructed to follow a post-treatment regimen. Specifically, patients were requested to apply both physical sunscreen with >10% zinc oxide and healing creams containing zinc and/or hyaluronic acid every 2 hours during waking hours for 48 to 96 hours following PDT treatment. Patients were also instructed to avoid prolonged sunlight and tanning beds for 48 hours after PDT. Patients were evaluated at clinical follow up within 2-4 weeks of PDT. If residual cancer existed, another PDT session was recommended in the next month. At follow up, patients were also evaluated for patient-reported symptoms of discomfort and clinician-confirmed signs of skin irritation.

The number of treatments required for clinical resolution ranged from 1 to 4 sessions (M = 2, SD = 0.82) (Table I). Of the 5 NMSC lesions on the face (cheek, jaw, and nose), an average of 2.4 sessions were required for resolution with a range of 2 to 4. The 4 NMSC lesions on the face that were incubated for 60 minutes required an average of 2.5 sessions. The 1 SCC of the scalp required 2 sessions for resolution. The SCCIS of the neck required 1 session and the SCC of the chest required 2 sessions. Of the lesions on the ear, an average of 1.5 sessions were required ranging from 1 to 2. None of the patients reported any irritation or adverse events and were compliant with the post-treatment instructions. No evidence of recurrence has been observed in the past 5 years.

DISCUSSION

The mechanism of PDT includes preferential absorption of the photosensitizer by malignant or premalignant cells. NMSC and AK cells have both higher rates of ALA uptake and higher rates of synthesis and accumulation of PpIX within the mitochondria. It has been shown that critical enzymes within the heme synthesis pathway are upregulated within malignant cells.[6] Animal models have exhibited preferential accumulation of PpIX in tissue of SCC and BCC.[7,8] Additionally, accumulation of PpIX within AKs has been shown within humans using noninvasive fluorescence monitoring.[9]

Successful use of PDT for BCC, SCC, and SCCIS has been documented in the literature.[5,10] Our retrospective case series similarly reports 10 cases of NMSC that resolved with an average of 2 sessions of blue light PDT with 10% ALA gel and range of 1 to 4 sessions. Notably, no evidence of recurrence occurred at > 5 years after the final treatment session. In the literature, a randomized controlled trial of 3 patients with Basal Cell Nevus Syndrome

with a total of 141 BCCs investigated the efficacy of ALA 20% solution with blue light and red light PDT. The patients reached an overall clearance rate of 98% with blue light and 93% with red light.[11] Given that PDT has been approved as a treatment for BCC in some countries, more data exist on PDT for BCC than for SCC. In another study of 112 biopsy-proven lesions of SCC and SCCIS in 55 patients treated with red light PDT with MAL cream, the overall clearance rate was 73.2% at 3 months and 53.6% at 2 years.[12] In our series, 4 SCC and 3 SCCIS lesions resolved with blue light PDT with 10% ALA gel with no clinical evidence of recurrence at 5 years.

A meta-analysis of 17 unique randomized controlled trials (RCTs) of PDT for BCCs and SCCs in adults showed that PDT was more likely to receive a "good" or "excellent" rating for cosmetic outcome than surgery or cryotherapy.[5] PDT may therefore offer a good option for NMSC lesions on the face or other cosmetically sensitive locations. Additionally, PDT has been studied extensively as an effective field cancerization therapy for AKs. While PDT with 10% ALA gel is approved for areas up to 20 cm^2, it has been demonstrated as safe and effective for surface areas 75-300 cm^2.[13] This suggests that PDT may be a good option for patients with significant UV damage and multiple NMSC within a contained area.

The main limiting factor for the use of PDT is pain during illumination. Multiple studies have been published suggesting protocols to reduce pain and burning during illumination. A bilaterally controlled intrapatient trial of 23 patients demonstrated that immediate illumination following ALA application resulted in significantly less pain than the conventional method of 1 hour incubation. At 3 months after treatment, lesion eradication was nearly identical between methods.[14] A randomized controlled intrapatient trial of 22 patients revealed that application of superpotent topical corticosteroid before and after treatment of AKs of the face and scalp reduced erythema 24 hours after treatment without affecting the efficacy of PDT.[15] In our reported case series, the patients were incubated with ALA gel for 90 minutes and subsequently illuminated for 16 minutes and 40 seconds. Overall, the patients tolerated the treatment well since they were compliant with a post-treatment regimen over the subsequent 48 hours. Patients were instructed to apply physical sunscreen and a healing cream every 2 hours during waking hours for the next 48 hours after the PDT session. The primary limitations in this case series were that only 10 patients were included, that only blue light illumination was utilized, and that a larger sample size is required for statistically significant conclusions. Given the efficacy and tolerability in this case series, without recurrence after 5 years, larger studies investigating recurrence rates after red light illumination as well as blue light illumination for BCC, SCC, and SCCIS are needed.

Conflicts of interest

Angela Yen Moore, MD, Kara Hurley, Stephen Moore, and Luke Moore have no disclosures.

REFERENCES

1. Tampa M, Sarbu MI, Matei C, et al. Photodynamic therapy: a hot topic in dermato-oncology. *Oncol Lett*. 2019;17(5):4085-4093. https://doi.org/10.3892/ol.2019.9939
2. Griffin LL, Lear JT. Photodynamic therapy and non-melanoma skin cancer. *Cancers*. 2016;8(10):98. https://doi.org/10.3390/cancers8100098
3. *AMELUZ (Aminolevulinic Acid Hydrochloride) Gel, 10% [Package Insert]*. US Food and Drug Administration; 2016.
4. Vegter S, Tolley K. A network meta-analysis of the relative efficacy of treatments for actinic keratosis of the face or scalp in Europe. *PLoS One*. 2014;9(6):e96829. https://doi.org/10.1371/journal.pone.0096829
5. Ou-Yang Y, Zheng Y, Mills KE. Photodynamic therapy for skin carcinomas: a systematic review and meta-analysis. *Front Med*. 2023;10:1089361. https://doi.org/10.3389/fmed.2023.1089361
6. Anand S, Ortel BJ, Pereira SP, Hasan T, Maytin EV. Biomodulatory approaches to photodynamic therapy for solid tumors. *Cancer Lett*. 2012;326(1):8-16. https://doi.org/10.1016/j.canlet.2012.07.026
7. Anand S, Rollakanti KR, Brankov N, Brash DE, Hasan T, Maytin EV. Fluorouracil enhances photodynamic therapy of squamous cell carcinoma via a p53-independent mechanism that increases protoporphyrin IX levels and tumor cell death. *Mol Cancer Ther*. 2017;16(6):1092-1101. https://doi.org/10.1158/1535-7163.MCT-16-0608
8. Anand S, Wilson C, Hasan T, Maytin EV. Vitamin D3 enhances the apoptotic response of epithelial tumors to aminolevulinate-based photodynamic therapy. *Cancer Res*. 2011;71(18):6040-6050. https://doi.org/10.1158/0008-5472.CAN-11-0805
9. Warren CB, Lohser S, Wene LC, Pogue BW, Bailin PL, Maytin EV. Noninvasive fluorescence monitoring of protoporphyrin IX production and clinical outcomes in actinic keratoses following short-contact application of 5-aminolevulinate. *J Biomed Opt*. 2010;15(5):051607. https://doi.org/10.1117/1.3484255
10. Farberg AS, Marson JW, Soleymani T. Advances in photodynamic therapy for the treatment of actinic keratosis and nonmelanoma skin cancer: a narrative review. *Dermatol Ther*. 2023;13(3):689-716. https://doi.org/10.1007/s13555-023-00888-1
11. Maytin EV, Kaw U, Ilyas M, Mack JA, Hu B. Blue light versus red light for photodynamic therapy of basal cell carcinoma in patients with Gorlin syndrome: a bilaterally controlled comparison study. *Photodiagnosis Photodyn Ther*. 2018;22:7-13. https://doi.org/10.1016/j.pdpdt.2018.02.009
12. Calzavara-Pinton PG, Venturini M, Sala R, et al. Methylaminolaevulinate-based photodynamic therapy of Bowen's disease and squamous cell carcinoma. *Br J Dermatol*. 2008;159(1):137-144. https://doi.org/10.1111/j.1365-2133.2008.08593.x
13. Moore AY, Moore S. Tolerability of photodynamic therapy using 10% 5-aminolevulinic acid hydrochloride gel for treating actinic keratoses on surface areas larger than 75cm^2. *J Clin Aesthet Dermatol*. 2020;13(9):45-48.

14. Kaw U, Ilyas M, Bullock T, et al. A regimen to minimize pain during blue light photodynamic therapy of actinic keratoses: bilaterally controlled, randomized trial of simultaneous versus conventional illumination. *J Am Acad Dermatol*. 2020;82(4): 862-868. https://doi.org/10.1016/j.jaad.2019.09.010

15. Wiegell SR, Petersen B, Wulf HC. Topical corticosteroid reduces inflammation without compromising the efficacy of photodynamic therapy for actinic keratoses: a randomized clinical trial. *Br J Dermatol*. 2014;171(6):1487-1492. https://doi.org/10.1111/bjd.13284