Photodynamic therapy for cutaneous squamous cell carcinoma in situ: Impact of anatomic location, tumor diameter, and incubation time on effectiveness

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Background: Photodynamic therapy (PDT) has been reported as a treatment for cutaneous squamous cell carcinoma in situ (SCCis), but only limited data are available on the effectiveness of PDT with aminolevulinic acid (ALA-PDT).

Objective: To review the outcomes of SCCis treated with ALA-PDT and examine factors associated with response.

Methods: A retrospective review identified 58 patients with 68 primary SCCis lesions treated with ALA-PDT and blue light illumination. Patient demographics, lesion features, treatment details, clinical response, and subsequent recurrence were extracted from medical record reviews.

Results: On completion of PDT the initial complete response rate was 77.9% and was not associated with the number of PDT treatments. On multivariate analysis factors associated with response were location on the face, tumor diameter <2 cm, and longer ALA incubation time. Lesions treated with a maximum incubation time of <3 hours had a 53.3% response compared with 84.9% for longer incubation. Subsequent recurrence of SCCis was noted in 7 of 53 cases (13.2%) at a median time of 11.7 months.

Limitations: This was a retrospective study performed at a single institution without systematic follow-up.

Conclusions: ALA-PDT may be an effective treatment for selected cases of SCCis. Effectiveness is impacted by anatomic location, tumor diameter, and ALA incubation time. (J Am Acad Dermatol 2020;82:1124-30.)

Key words: aminolevulinic acid; Bowen disease; humans; photodynamic therapy; retrospective studies; skin neoplasms; squamous cell carcinoma in situ; treatment outcome.

Cutaneous squamous cell carcinoma in situ (SCCis; also known as Bowen disease) is a slow-growing, intraepidermal, keratinocyte-derived malignancy.[1] Treatment options for SCCis include destructive modalities (cryotherapy or curettage), medical therapy (topical imiquimod or 5-fluorouracil), photodynamic therapy (PDT), and surgical excision or Mohs micrographic surgery.[2-4] PDT consists of topical application of a prodrug such as aminolevulinic acid (ALA) or methyl aminolevulinate followed by a defined incubation period in which the medication is absorbed and converted to protoporphyrin IX via cellular metabolism. Protoporphyrin IX is then activated by treatment with visible light, which generates free radicals, cytotoxicity, and cell death.[5] Several clinical trials and retrospective studies of SCCis have reported cure rates with PDT ranging from 50% to 100%,[3,6-12] and

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some have suggested that it is comparable with or superior to medical or destructive therapy.[8,9]

PDT has several potential advantages over other therapies, such as low morbidity, excellent functional and cosmetic outcomes, short duration of treatment, and ability to treat surrounding field cancerization.[13-15] However, clinical use of PDT for SCCis is hindered by the lack of standardized treatment protocols or outcomes data. In the United States the most common form of PDT administration is with ALA (ALA-PDT) and blue light illumination, but most published studies for SCCis have used methyl aminolevulinate and red light illumination. Moreover, it is unclear whether other tumor or treatment variables affect response to PDT. Data are conflicting on whether tumor size[8,11,12,16,17] or anatomic location[8,18-22] influences response. The number of PDT treatments and ALA incubation time have also been variably reported to affect the clearance of malignant and premalignant lesions.[8,9,23] Our objective in this study was to define the response of SCCis to ALA-PDT in a real-world setting and to assess the impact of various lesion and treatment variables on effectiveness.

CAPSULE SUMMARY

- There are limited data on the effectiveness of photodynamic therapy with aminolevulinic acid and blue light for cutaneous squamous cell carcinoma in situ.
- In this retrospective study a longer incubation time with aminolevulinic acid, smaller tumor diameter, and location on the face were all associated with increased effectiveness of photodynamic therapy.

METHODS

Patient selection and treatment

This was a retrospective study of patients evaluated from 2013 to 2017 at Yale Dermatologic Surgery, Yale University School of Medicine. The study was approved by the Yale Institutional Review Board (IRB number 2000024076).

All patients had clinically identifiable SCCis confirmed with prior biopsy. Cases were excluded if the lesion had been previously treated surgically or if the patient had received any field treatment (PDT, topical fluorouracil, imiquimod, or ingenol mebutate) to the area in the last year.

The treatment protocol consisted of topical application of 20% ALA solution to the lesion and surrounding skin followed by a defined incubation period and subsequent illumination by noncoherent blue light at 10 J/cm^2. Incubation time and total number of PDT treatments were determined by the treating physician. Hyperkeratotic lesions were treated with curettage before ALA application at the discretion of the treating physician. For patients who received multiple treatments, the interval between treatments was 1 to 8 months (median, 2.1).

Tumor response was defined by clinical examination within 3 months after completion of all PDT treatments. Recurrence was defined by pathologic confirmation of SCCis in the same anatomic location. For disease-free individuals, the date of last follow-up with documented absence of disease was considered the last follow-up.

Data extraction

The electronic medical record was reviewed and the following variables recorded in a deidentified manner: age at the time of first treatment, gender, Fitzpatrick skin type, immunosuppression (if any), anatomic location of lesion, and tumor size. If the tumor diameter was not directly specified in the electronic medical record, clinical photographs were reviewed to determine whether the diameter was less than or at least 2 cm. For all treatments, dates, incubation time, and use of occlusion during treatment were recorded. For post-treatment follow-up, visit dates and clinical responses were recorded.

Statistical analysis

Correlation of patient, tumor, and treatment variables with clinical response was assessed using χ^2 tests (for categorical variables), unpaired t test, or Mann-Whitney U test (for continuous variables) as well as univariate and multivariate logistic regression using Stata, version 15 (StataCorp LLC, College Station, TX). To determine correlation between occlusion and incubation time, a Spearman's rank correlation coefficient was used.

RESULTS

Sixty-eight cases of SCCis from 58 patients were included in the study (Table I). Cases presented in patients with a mean age of 78.4 years (range, 50-98), and 48.5% of cases were in men. Only 8 cases (11.8%) were from immunosuppressed patients, and 2 of these were from solid organ transplant recipients. Over half of the lesions (55.9%) were located on the face, with the remainder on the scalp (25%), extremities (11.8%), and other sites. Twenty-eight lesions (41.2%) were ≥2 cm in maximum diameter. For the 60 lesions with exact measurements, the mean diameter

Abbreviations used:

ALA: aminolevulinic acid
ALA-PDT: aminolevulinic acid photodynamic therapy
CR: complete response
PDT: photodynamic therapy
SCCis: squamous cell carcinoma in situ

was 1.7 cm (median, 1.5 cm; range, 0.3-7.0). Most cases (51 lesions, 75%) had gross residual tumor evident at the time of first PDT treatment. Forty-two lesions (61.8%) were treated with a single PDT treatment, 23 lesions (33.8%) had 2 treatments, 2 lesions had 3 treatments, and 1 lesion had 4 treatments. Incubation period with ALA ranged from 1 to 16.5 hours, with 95.1% of treatments using an incubation period of 2 to 5 hours.

Initial complete response (CR) was defined as the absence of a residual lesion on clinical examination within 3 months after completion of all PDT sessions (Fig 1). Among 68 cases of SCCis treated with PDT, 53 (77.9%) achieved CR. The number of PDT treatments was not associated with CR: 81.0% of cases treated with 1 PDT session had CR, and 73.1% of cases treated with at least 2 PDT sessions had CR (Supplemental Fig 1, *A*; available at https://doi.org/10.17632/nn35dsmpf6.1).

We identified several patient-, tumor-, and treatment-related variables that were associated with CR. Tumor diameter was significantly associated with CR: Lesions <2 cm had a CR of 87.5%, compared with a CR of 64.3% for lesions ≥2 cm (P = .023) (Fig 2, *A*). Anatomic location also affected response. Lesions on the face had a CR of 86.8% (33/38), compared with 66.7% (20/30) for all other locations (P = .046) (Fig 2, *B*). For nonfacial lesions, 12 of 17 lesions on the scalp (70.6%) had a CR, compared with 2 of 2 lesions on the ear, 0 of 1 lesion on the neck, 2 of 2 lesions on the trunk, and 2 of 4 lesions each on the upper and lower extremities. Older patients exhibited a decreased response to PDT. When lesions were grouped into 4 age quartiles, lesions arising in patients in the oldest quartile (88-98 years) had a lower CR (52.9%, 9/17 lesions) than all other lesions, with a CR of 86.3% (44/51) for lesions arising in patients aged 50 to 87 years (P = .020) (Fig 2, *C*). Responses in the youngest 3 quartiles of age were not significantly different from each other. Gender and immunosuppression were not associated with CR.

The most important treatment-related variable affecting CR was ALA incubation time. We grouped cases according to maximum incubation time for any PDT treatment. Cases with <3-hour maximum incubation time exhibited the lowest CR (53.3%, 8/15 cases) compared with those with 3- to 3.99-hour incubation times (83.3%, 25/30 cases) and ≥4-hour incubation times (87.0%, 20/23 cases; P = .032) (Fig 2, *D*). Similar results were observed when we restricted the analysis to response after the first PDT session only, with a CR of 27.8%, 74.1%, and 71.4% for incubation times of <3 hours, 3 to 3.99 hours, and ≥4 hours, respectively (P = .006) (not shown). Occlusion of the treated site with an impermeable dressing was not significantly associated with CR (85.7% [18/21 cases] with occlusion vs 74.5% [35/47 cases] without occlusion). However, occlusion and incubation time were strongly correlated (Supplemental Fig 2; https://doi.org/10.17632/nn35dsmpf6.1), which precluded an independent analysis of the effect of occlusion on response.

Univariate logistic regression analysis indicated that tumor diameter and ALA incubation time were significantly associated with CR, whereas age and anatomic location approached, but did not reach, statistical significance (Table II). Using these 4 variables in a multivariate analysis, the strongest

Table I. Squamous cell carcinoma in situ lesion characteristics and PDT treatment parameters (n = 68 lesions, n = 58 patients)

Characteristic	Value
Mean age, y (range)	78.4 (50-98)
Lesions in men	33 (48.5)
Lesions in immunosuppressed	8 (11.8)
Solid organ transplant recipient	2 (2.9)
Anatomic location	
Face	38 (55.9)
Other	30 (44.1)
Scalp	17
Ear	2
Neck	1
Trunk	2
Upper extremity	4
Lower extremity	4
Median tumor diameter, cm (range)	1.5 (0.3-7.0)
Lesions ≥2 cm	28 (41.2)
PDT treatments	
1	42 (61.8)
2	23 (33.8)
3-4	3 (4.4)
Maximum incubation time from PDT	
2-2.99 h	15 (22.1)
3-3.99 h	30 (44.1)
≥4 h	23 (33.8)
Occlusion from ≥1 PDT session	21 (30.9)
Occlusion during first PDT session	20 (29.4)

Values are n (%) unless otherwise defined. Age, gender, and immunosuppression are presented by number of lesions/cases.
PDT, Photodynamic therapy.

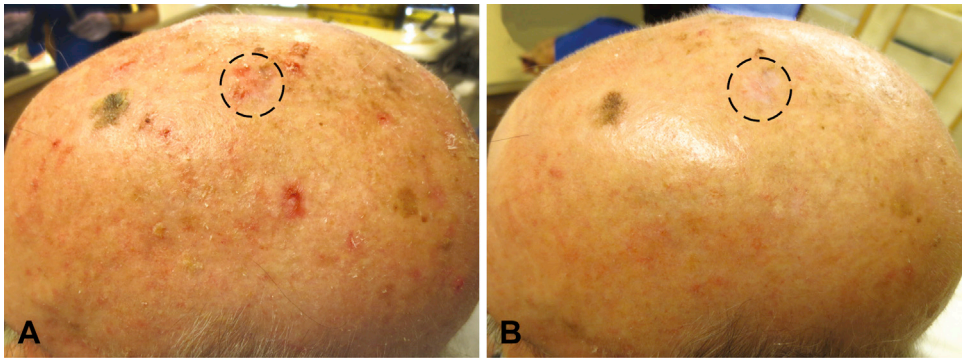

Fig 1. Squamous cell carcinoma in situ with complete response to photodynamic therapy (PDT). **A**, Visible, biopsy-confirmed lesion of squamous cell carcinoma in situ (*circled*) on the scalp before PDT treatment. **B**, Complete response with clinical resolution of lesion (*circled*) 2 months after a single PDT treatment. There is also clearance of surrounding actinic keratoses in the treated field.

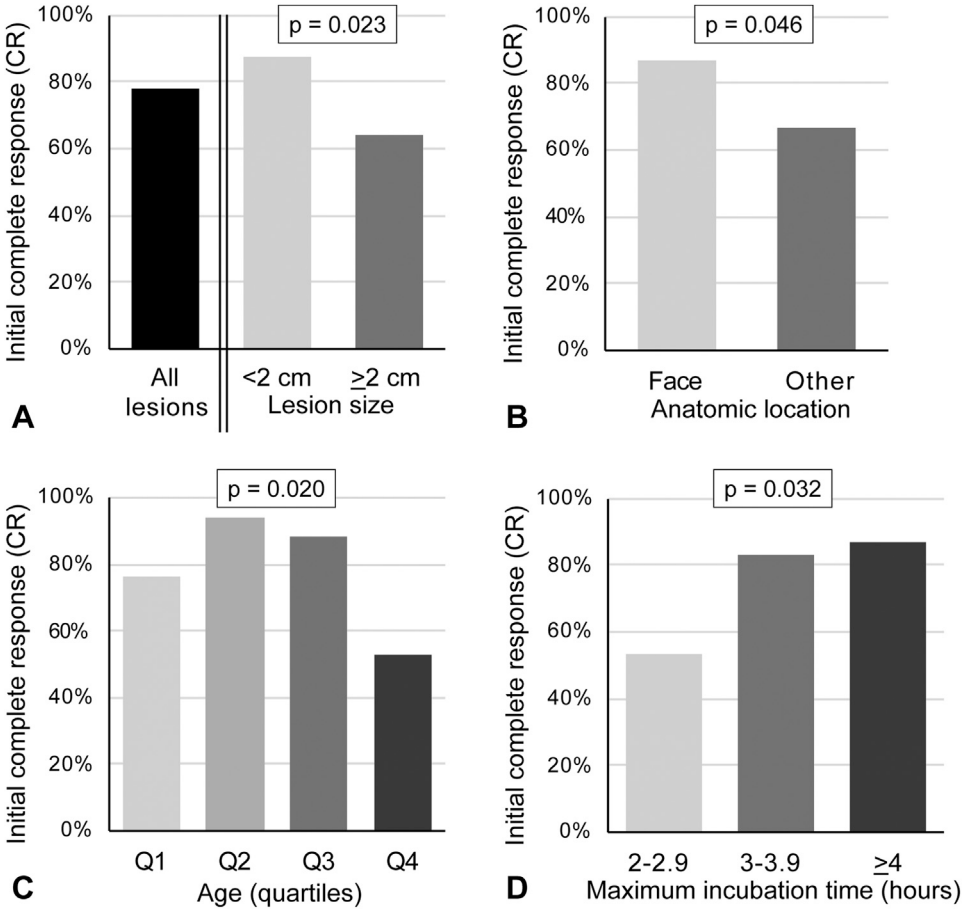

Fig 2. Factors affecting response of squamous cell carcinoma in situ (SCCis) to photodynamic therapy (PDT). Initial complete response (CR) of SCCis after completion of PDT treatment (% of lesions). **A**, CR of all lesions and CR according to maximum tumor diameter. **B**, CR according to anatomic location on face versus all other sites. **C**, CR according to patient age quartiles (Q1, 50-69.5; Q2, 69.5-81; Q3, 82-87; Q4, 88-98). **D**, CR according to maximum incubation time from any PDT. *P* values were calculated using χ^2 test.

Table II. Factors associated with initial complete response

Variable	Univariate odds ratio	Multivariate odds ratio
Age	0.949 (P = .088)	0.966 (P = .297)
Tumor diameter ≥2 cm	0.257 (P = .028)	0.246 (P = .047)
Anatomic location (face vs all other)	3.300 (P = .053)	6.311 (P = .019)
Maximum incubation time from PDT session (≥4 vs 3-3.99 vs 2-2.99 h)	2.569 (P = .028)	3.096 (P = .037)
Male gender	1.558 (P = .456)	
Immunosuppression	0.417 (P = .273)	
No. of photodynamic therapy treatments (1-4)	0.754 (P = .522)	

Age was analyzed as a continuous variable. Four variables of potential significance were included in the multivariate analysis.

predictor of CR was anatomic location on the face (odds ratio, 6.311; P = .019), followed by maximum PDT incubation time (odds ratio, 3.096; P = .037) and tumor diameter ≥2 cm, which was negatively correlated with CR (odds ratio, 0.246; P = .047). Tumor diameter was also negatively correlated with CR when diameter was analyzed as a continuous, rather than dichotomous, variable (odds ratio, 0.5; P = .011). Similar associations of tumor diameter and PDT incubation time with CR were observed when the multivariate analysis was restricted to response after the first PDT treatment only (not shown).

Among patients with initial CR, median follow-up duration was 9.7 months. Durable response, defined as persistence of CR at the final follow-up, was achieved in 46 of 68 cases (67.6%) and was not associated with number of PDT treatments (Supplemental Fig 1, *B*; available at https://doi.org/10.17632/nn35dsmpf6.1). Recurrence, defined as biopsy-confirmed SCCis at the site of the original lesion, was identified in 7 of 53 cases (13.2%) with initial CR. Median time to recurrence was 11.7 months (range, 7.7 to 33.4). None of the examined variables (including age, tumor diameter, anatomic location, presence of immunosuppression, ALA incubation time, or follow-up duration) was significantly associated with recurrence (Supplemental Table I; available at https://doi.org/10.17632/nn35dsmpf6.1).

DISCUSSION

PDT has been reported as a treatment for SCCis[6-12] but is not approved for this indication in the United States. One challenge in interpreting the data on PDT for SCCis is the lack of consistent treatment protocols. Published reports have varied in the type of photosensitizer used, incubation period, light source for illumination, number of treatments, and lesion characteristics such as size and location. To our knowledge only 1 previous study of 6 patients has reported the use of ALA-PDT with blue light illumination for SCCis.[24] In the retrospective study presented here we demonstrate that ALA-PDT can be an effective treatment for selected cases of SCCis, with an initial clinical CR comparable with results from other studies. We also determined that specific tumor and treatment variables such as tumor diameter, anatomic location, and incubation time are strongly associated with clinical response.

Unlike tumor diameter or anatomic location, photosensitizer incubation time is a variable that can be manipulated to optimize treatment success. We found that incubation times of 3 hours or more were significantly associated with CR, presumably because of greater protoporphyrin accumulation. Protoporphyrin IX accumulates in actinic keratoses after photosensitizer application in a linear fashion over the first 2 to 3 hours of incubation but then reaches a plateau.[25,26] Similarly, increased incubation time correlates with improved clinical response of actinic keratoses.[23] Data on the impact of incubation time on treatment response in SCCis are limited. One study of 15 cases of SCCis compared the impact of 5-hour (n = 6) versus 16-hour (n = 9) incubation with ALA. At 24 weeks response rates favored the longer incubation time (77.8% vs 33.3%) but were not statistically significant.[27] Curettage of lesions before ALA application and occlusion during ALA incubation are also likely to affect absorption and therefore effectiveness of PDT. Because of a lack of data on curettage and the strong correlation of occlusion with incubation time in our study, we were not able to independently assess the effects of curettage and occlusion. Additional studies are needed to determine the optimal protocol for ALA-PDT treatment of SCCis.

In our study tumors ≥2 cm were 4-fold less likely to respond to PDT, which has been previously reported in most studies.[8,11,12,16] Larger diameter tumors may be more resistant to PDT for a variety of reasons, including more aggressive inherent biology,[28,29] inconsistent exposure of the entire lesion to photosensitizer or illumination, potential for occult invasive SCC not detected on biopsy,[30,31] or potential for histologically thicker lesions. Although SCCis has been reported to invade hair follicles, the low rate of deep follicle invasion

(<12.5%) and the lack of association of follicular invasion with tumor diameter suggest that invasion of hair follicles is not likely to be the critical factor in response of SCCis to PDT.[32] Regardless of the mechanism, SCCis with diameter ≥2 cm may have a suboptimal response to ALA-PDT.

SCCis located on the face was significantly more likely than lesions on other locations to respond to PDT. Perhaps because of the small number of cases of SCCis at other locations, there was no significant difference in response between different nonfacial sites. Anatomic location has not been definitively shown to impact response of SCCis to PDT in previous studies.[8,18] In contrast, multiple studies have shown that actinic keratoses on the upper or lower extremities are less likely to respond to PDT,[33,34] in part owing to lower physiologic temperature and impaired temperature-dependent protoporphyrin IX accumulation.[35] It is possible that the response of nonfacial SCCis to PDT may be enhanced by the application of exogenous heat, similar to what has been reported for premalignant lesions.[36,37] The number of PDT treatments in our cohort did not significantly impact response, perhaps owing to selection bias, because lesions resistant to initial PDT may have been more likely to be treated with additional PDT. The decision to perform 1 versus multiple PDT treatments in our study was made by the treating physician because of the lack of prior studies on ALA-PDT with blue light. Although most studies of PDT for SCCis use 2 treatment sessions with red light, others have documented response rates of 80% after a single treatment,[38] and there is a lack of direct comparison between 1 versus multiple treatments, highlighting the need for further investigation in this area.

This single-center study is limited by its retrospective design and lack of systematic follow-up. However, median follow-up of patients with CR was nearly 1 year, and we were able to assess for durable response and disease recurrence. Seven recurrences (13.2%) were observed in our cohort between 7 and 33 months after PDT. None of the variables we examined was significantly associated with recurrence. Although many studies of PDT for SCCis have limited follow-up duration, delayed recurrences have been previously reported. One study found that half of the recurrences presented after 12 months.[39] Ongoing screening for recurrence after PDT for SCCis thus is recommended.

ALA-PDT with blue light may be an effective, well-tolerated treatment for selected cases of SCCis. PDT may provide the additional benefit of treating premalignant lesions in the surrounding actinically damaged field.[15] Field therapy of precursor lesions with topical fluorouracil has been shown to reduce the risk of subsequent SCC,[40] and repeated cycles of PDT have been suggested to prevent formation of carcinomas in high-risk patients with multiple lesions.[41] In this fashion PDT may both treat existing SCCis and prevent subsequent lesions, but additional investigation is required to define the nature of this effect. In our cohort we identified specific factors such as anatomic location, tumor diameter, and ALA incubation time that are significantly correlated with treatment success. These factors should be included in future studies to refine the effectiveness of PDT for SCCis.

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