Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2022 Feb 15; 10(F):86-89.
https://doi.org/10.3889/oamjms.2022.8543
eISSN: 1857-9655
**Category:** *F - Review Articles*
***Section:*** *Narrative Review Article*



# The Efficacy of Topical Photodynamic Therapy in Precancerous Lesions of the Skin: A Literature Review

Imam Budi Putra*, Nelva Karmila Jusuf, Calvina Theresia

*Department of Dermatology and Venereology, Faculty of Medicine, Universitas Sumatera Utara, Universitas Sumatera Utara Hospital, Medan, Indonesia*

**Edited by:** Ksenija Bogoeva-Kostovska
**Citation:** Putra IB, Jusuf NK, Theresia C. The Efficacy of Topical Photodynamic Therapy in Precancerous Lesions of the Skin: A Literature Review. Open-Access Maced J Med Sci. 2022 Feb 15; 10(F):86-89. https://doi.org/10.3889/oamjms.2022.8543
**Keywords:** Topical photodynamic therapy; Precancerous skin lesions; Actinic keratosis; Bowen's disease
***Correspondence:** Imam Budi Putra, Department of Dermatology and Venereology, Faculty of Medicine, Universitas Sumatera Utara, Universitas Sumatera Utara Hospital, Medan, Indonesia.
E-mail: imam_65@yahoo.com
**Received:** 06-Jan-2022
**Revised:** 28-Jan-2022
**Accepted:** 05-Feb-2022

**Funding:** This research did not receive any financial support
**Competing Interest:** The authors have declared that no competing interest exists


**Abstract**

Precancerous skin lesions are associated with high probability of malignant transformation to squamous cell carcinoma. Early detection and management are necessary to improve prognosis and outcomes. Literatures showed that topical photodynamic therapy (PDT) is a promising treatment method which can be successfully applied in several conditions in dermatology. This study aims to review the efficacy of topical PDT for various precancerous lesions in dermatology, such as actinic keratosis, Bowen disease, and Bowenoid papulosis.

## Introduction

Precancerous skin lesions are associated with high probability of malignant transformation to squamous cell carcinoma. Early detection and management are necessary to improve prognosis and outcomes. Among many modalities of treatments available, utilization of topical photodynamic therapy (PDT) is increasing in trends due to its non-invasive technique and good safety profile [1].

The literatures showed that topical PDT is a promising treatment method which can be successfully applied in several conditions in dermatology, including precancerous lesions such as actinic keratosis (AK), Bowen disease (BD), and other skin disorders such as acne vulgaris, viral warts, and extramammary Paget's disease. This study aims to review the efficacy of topical PDT for various precancerous lesions in dermatology [2], [3], [4].

## Topical PDT

In general, topical PDT requires three main components; a photosensitizer, light source, and oxygen. Successful PDT therapy depends on preferential localization of the photosensitizer in the diseased tissue and high yield of reactive oxygen species produced on photoexcitation of photosensitizer which destroys the diseased tissues [5].

Several studies also showed the efficacy of pre-treatments before topical PDT procedures using several techniques such as curettage, superficial shaving, laser, surgical resection, plum-blossom needles, and microneedles. These pre-treatments were associated with improved efficacy and reduced recurrence in several reports [6], [7], [8].

### *Photosensitizers*

There are several options of photosensitizers available in settings of topical PDT. At present,

the second-generation photosensitizers such as 5-aminolevulinic acid (ALA), a biological precursor of protoporphyrin IX and its methylated ester, and methyl aminolevulinate (MAL) are the photosensitizers more widely used in dermatology [9].

### *Light sources*

Types of lights commonly used in PDT include red light, blue light, and infrared light. Among those, blue light penetrates to the tissue the least. Optimal therapeutic wavelength of the light source for PDT is between 600 and 800 nm. This wavelength light source is preferred due to the deeper penetration of the light in tissue which allows treatment of target tissue. Use of longer wavelengths (>800 nm) is not practical due to their lack of photodynamic reactions [10].

## Efficacy of Topical PDT in Various Precancerous Skin Lesions

### *Actinic Keratosis (AK)*

AK is the most common precancerous lesion of the skin. AK may present with irregular, red, scaly papules, or plaques which arises in chronically ultraviolet exposed area. If the left untreated, it is associated with 5 times increased risk of progression to invasive carcinoma. Therefore, early recognition of AK lesions and prompt intervention is necessary [11], [12].

Various treatment modalities are available for the treatment of AK. In individual AK lesions, lesion-directed therapies such as cryotherapy, curettage, and surgery might be preferred. Whereas in multiple AK lesions, field-directed therapies such as topical medications, light-based therapies, and laser resurfacing may have greater advantage [13].

Topical PDT is widely used in treating AK; despite its cost, this procedure is proven to be safe, effective, and associated with excellent cosmetic outcome. Several studies regarding the application of topical PDT in AK patients are summarized in Table 1 [14], [15], [16], [17], [18].

### *Bowen Disease (BD)*

BD is a squamous cell carcinoma *in situ*, first described in 1912. This entity is associated with 3–5% risk of invasive carcinoma transformation [20]. BD is characterized by slow-growing well-demarcated erythematous plaque with scaly surface. Several treatment modalities for BD are cryotherapy, curettage with cautery, excision, 5-fluorouracil (5-FU), radiotherapy, laser, PDT, imiquimod, and diclofenac 3% gel [21], [22].

In Table 2, we summarized outcomes of several studies concerning the application of topical PDT in patients with BD [23], [24], [25].

In RCTs, topical PDT is shown to be equivalent or superior in efficacy and healing compared to cryotherapy and 5-FU. It may be of particular benefit for large-sized lesions or lesions located at difficult sites, but this procedure is costly. PDT for premalignant skin lesions has now been approved as an interventional procedure by the National Institute for Health and Clinical Excellence in the U.K., and MAL-PDT has been approved by the European Medicines Authority for the treatment of BD [3], [26].

### *Bowenoid papulosis (BP)*

BP also termed “vulvar intraepithelial neoplasia (VIN)” in the vulva and termed “penile

**Table 1: Summary of studies regarding topical PDT interventions in AK patients**

| Authors | Interventions | Follow-up | Results |
|---|---|---|---|
| Pariser *et al.* [14] | A randomized study of 80 AK patients, 42 undergo topical MAL-PDT, and 38 in the placebo group | 3 months | Excellent or good cosmetic outcome was reported in more than 90% of patients treated with MAL |
| Morton *et al.* [15] | A multicenter, randomized, and split-face study of 119 subjects with 1501 AK lesions. All subjects received both topical MAL-PDT and cryotherapy randomly allocated to either side of the face/scalp | Week-12, Week-24 | At week-12, percentage lesion reduction from baseline: 86.9% (MAL-PDT) versus 76.2% (cryotherapy); P<0.001. At week-24, both treatment groups showed a high rate of cured lesions (89.1% for MAL-PDT vs. 86.1% for cryotherapy). The MAL-PDT group was associated with superior cosmetic outcomes |
| Kaufmann *et al.* [16] | A multicenter, controlled, randomized, open, intraindividual, and right-left comparison of 121 patients with 1343 AK lesions. All subjects received both one session of MAL-PDT and cryotherapy on either side of the body | week-12, week-24 | At week-24, significantly higher mean percentage reduction in cryotherapy group: 78% for MAL-PDT and 88% for cryotherapy (p=0.002). While, significantly better cosmetic outcome assessed in the MAL-PDT group 79% versus 56% in cryotherapy group (p<0.001) |
| Pariser *et al.* [17] | A multicenter, double-blind, and randomized study. A total of 49 patients with 363 AK lesions had 16.8% MAL cream applied under occlusion for 3 h, and 47 patients with 360 AK lesions had vehicle cream similarly applied. All subjects undergone two sessions of PDT | 3 months | Efficacy of MAL-PDT group was significantly superior compared to vehicle-PDT with respect to lesion complete response 86.2% versus 52.2% (p<0.0001) |
| Held *et al.* [18] | One session of topical PDT *plus* imiquimod 5% cream×3/ week afterward. | 7–11 months | Out of three cases reported, two showed partial clearance and one showed no response |
| Wollina *et al.* [19] | A single-center, prospective, and clinical trial with a total of 30 patients with 148 AK lesions. All subjects undergone between 1 and 9 PDT sessions | 6 months | A complete clearance was achieved in 93.3%, and>90% clearance in 6.7% |

**Table 2: Outcomes of studies concerning topical PDT interventions in BD patients**

| Authors | Interventions | Follow-up | Results |
|---|---|---|---|
| Zaar *et al*. [23] | A retrospective and observational study of 423 BD lesions in 335 patients. About 87% of subjects completed one MAL-PDT session and 13% undergone two MAL-PDT sessions | Mean 11.2 months | Clinical response rate 77.5%, with 18.3% recurrence rate at an average of 11.2 months follow-up |
| Truchuelo *et al*. [24] | A retrospective, observational and descriptive study of 47 patients with 51 lesions of BD. All patients received two sessions topical MAL-PDT 1 week apart | Mean 16.61 months | Complete response rate was achieved in 76.09% of the lesions |
| Morton *et al*. [25] | A multicenter, randomized, and placebo-controlled study of 225 patients from 40 dermatology centers in Europe. Subjects were divided into topical MAL-PDT (two sessions), placebo-PDT, cryotherapy, and topical FU groups | 3–12 months after last treatment | Complete response rate in MAL-PDT group was superior than cryotherapy (80% vs. 67%; p=0.047), and better than fluorouracil group (80% vs. 69%; p=0.19). Cosmetic outcome at 3 months was good or excellent in 94% (MAL-PDT) versus 66% (cryotherapy) and 76% (FU) and was maintained until 12 months follow-up |

intraepithelial neoplasia" (PIN) in the penis [27]. BP is characterized by circumscribed, round, and usually multiple red-brown papules. Many reports demonstrate that this disease is caused by human papilloma virus (HPV) infection. Thus, it is potentially responsive to PDT [28], [29].

This entity represents a form of squamous cell carcinoma *in situ*, very often associated to the oncogenic high-risk HPV types 16, 18, 31, and 33 [30]. Transformation into invasive squamous cell carcinoma is rare and occurs in <1% of cases, especially in immunocompromised individuals [31].

A study by Che *et al*. investigated 200 BP cases; subjects were divided into 5-ALA PDT group and control group (treated with either radiofrequency cauterization, microwave ablation, or surgical resection). All lesions in the 5-ALA PDT treated group were cleared after therapy, with no recurrence at the 1-year follow-up; however, 20% of patients in the control group showed recurrence after 1 year [32].

Due to its efficacy, safety profile, low risk of scarring, and its capacity to be applied in difficult sites, especially in cases like BP which predilection sites are in penile and vagina, topical PDT has become one of the preferred modalities when BP is suspected. The major problem with this modality is pain during illumination, but it usually disappears after stopping the illumination [33].

## Summary

Topical PDT is a well-tolerated treatment and appears to be an effective method with good safety profile, low risk of scarring, and excellent cosmetic outcomes in the treatment of precancerous skin lesions such as AK, BD, and BP. Pre-treatments before topical PDT procedures are associated with improved efficacy and reduced recurrence in several reports.

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