Photodynamic therapy: A hot topic in dermato-oncology (Review)

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Abstract. Photodynamic therapy (PDT) is a modern, non-invasive therapeutic method used for the destruction of various cells and tissues. It requires the simultaneous presence of three components: a photosensitizer (PS), a light source and oxygen. Precancerous skin lesions are conditions associated with a high likelihood of malignant transformation to squamous cell carcinoma. Data available so far indicate that PDT is a promising treatment method which can be successfully employed in several medical fields including dermatology, urology, ophthalmology, pneumology, cardiology, dentistry and immunology. Numerous authors therefore have studied this technique in order to improve its efficacy. As a result, significant advancement has been achieved with regard to PSs and drug delivery systems. Substantial progress was also obtained with respect to PDT for the treatment of precancerous skin lesions, several authors focusing their efforts on the study of daylight-PDT and on identifying methods of decreasing technique-related pain. This review reports on the most recent findings in PDT, with emphasis on cutaneous precancerous lesions.

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Abbreviations: PDT, photodynamic therapy; ROS, reactive oxygen species; AK, actinic keratosis; SCC, squamous cell carcinoma; PS, photosensitizer; $^3O_2$, triplet oxygen; $O2^{\cdot-}$, superoxide anion; OH, hydroxyl radical; $^1O_2$, singlet oxygen; HpD, hematoporphyrin derivative; ALA, 5-aminolevulinic acid; MAL, methyl aminolaevulinate; PpIX, protoporphyrin IX; UCNPs, upconversion nanoparticles; NIR, near infrared; MRI, magnetic resonance imaging; c-PDT, conventional photodynamic therapy; D-PDT, daylight photodynamic therapy; HAL, hexylaminolaevulinate, RCM, reflectance confocal microscopy; BD, Bowen's disease; EQ, erythroplasia of Queyrat; 5-FU, 5-fluorouracil; HPV, human papilloma virus; Er:YAG AFL, erbium:yttrium-aluminium-garnet ablative fractional laser; AC, actinic cheilitis; LS, lichen sclerosus

Key words: photodynamic therapy, precancerous lesions, squamous cell carcinoma, actinic keratosis, actinic cheilitis

Contents

1. Introduction

Photodynamic therapy (PDT) is a relatively new, non-invasive therapeutic method used for the destruction of various cells and tissues consisting in the administration of a photosensitizing drug followed by irradiation of light and generation of reactive oxygen species (ROS) which lead to cell death. It has been employed in several medical fields including dermatology, urology, ophthalmology, pneumology, cardiology, dentistry and immunology (1-4). Moreover, antimicrobial and antiviral PDT have been found useful for the treatment of various infectious diseases, water sterilization and inactivation of pathogens in blood products, among others (1).

Precancerous skin lesions are conditions associated with a high likelihood of malignant transformation to squamous cell carcinoma (5,6). The lesions may exhibit increased mitotic rate, abnormal mitotic figures, nuclear pleomorphism or abnormal differentiation (6). Some of the lesions, such as actinic keratoses (AK), have minimal atypia, while others, such as Bowen's disease, are *in situ* squamous cell carcinomas (SCCs) (6).

The most important risk factors involved in the development of precancerous skin lesions are exposure to UV radiation, immunosuppression, fair skin type and genetic predisposition (7-15).

2. Photodynamic therapy - generalities

PDT requires the simultaneous presence of three components: a photosensitizer (PS), a light source and oxygen (16). The PS preferentially accumulates in tumor cells and in macrophages. When the PS is exposed to light of specific wavelength it becomes activated to the short-live (nanoseconds) excited singlet state. This state can decay to the ground state or it can undergo intersystem crossing to the long-live (microseconds) triplet state. The PS in the triplet state interacts with the surrounding molecules through two types of reactions. In type I reactions, either a hydrogen atom is abstracted, or an electron is transferred between the substrate and the PS and free radicals are produced. In type II reactions, the PS interacts with molecular oxygen, also known as triplet oxygen ($^3O_2$), and produces ROS, including superoxide anion ($O_2^{\cdot -}$), hydroxyl radical (OH) and singlet oxygen ($^1O_2$) (4,17,18). ROS, especially singlet anion, are very harmful for the surrounding cells and are responsible for the destructive effects of PDT (16). Depending on factors such as type and dose of PS, localization of PS, intensity and wavelength of light and oxygen concentration (19), PDT induces cell death through autophagy, apoptosis or cellular necrosis (1,16,19,20).

The history of PDT is long and marked by several important events. Even though ancient civilizations already knew that various plants could be combined with sunlight to treat skin diseases like vitiligo and psoriasis (21,22), the rediscovery and mechanism elucidation of PDT only occurred at the beginning of the 20th century (23). In 1900, Raab and von Tappeiner first observed an *in vitro* photodynamic effect and in 1904 von Tappeiner coined the term 'photodynamic' (24,25). In 1903 Niels Finsen was awarded the Nobel Prize for his contribution to the treatment of lupus vulgaris with concentrated light radiation (26,27) and in 1929 Hans Fischer received the Noble Prize for the examination of porphyrins (26). The discovery of hematoporphyrin derivative (HpD) in 1960 by Lipson *et al* (28) and photofrin by Dougherty *et al* are also key moments in the history of PDT (26,29).

Since PDT showed promising results in several medical fields, the subject captured the interest of numerous authors in recent years and extensive research was carried out in the attempt to improve the method. Our objective is to look over the most recent findings in PDT, with emphasis on cutaneous precancerous lesions.

3. Updates in PDT components

As mentioned before, PDT requires the presence of three components: light, PS and oxygen. A wide range of light sources can be used for PDT, including light emitting diodes, lasers and fluorescent lamps (30). Blue light is preferred for the maximum absorbance while red and infrared radiations best penetrate the tissues. However, only light up to 800 nm can generate singlet oxygen. The light source should be chosen based on PS absorption, disease characteristics and costs (30,31).

Several agents have been developed and studied in the attempt to identify ideal PS. Hematoporphyrin derivative and photofrin are first generation PSs. They have several limitations, including a complex composition and low light absorption rate (26). Hence, there was a real need to identify new PS. The second-generation PS were therefore developed. Most have a cyclic tetrapyrrolic structure and are represented by porphyrins and porphyrin analogs, chlorins, bacteriochlorins, phthalocyanines and metallo-phthalocyanines (1,32-35). 5-Aminolevulinic acid (ALA), a biological precursor of protoporphyrin IX (PpIX) and its methylated ester, methyl aminolaevulinate (MAL), have been widely used in dermatology (30). Mono-L-aspartyl chlorin e6 (NPe6), temoporfin and hexylpyropheophorbide (HPPH) have a chlorin structure and have been used in head and neck cancer, bile duct cancer, brain cancer, lung cancer and sarcoma (31). Second-generation PS are pure compounds, are well absorbed in the range of 650-800 nm and are less toxic than first generation PS. However, the degree of selectivity for the target tissue and the insufficient depth of treatment are the main limitations of these agents (1,4).

Third generation PS are currently being developed to improve PDT outcomes. Nanotechnology in PDT and gene engineering mediated PDT are therefore intensely researched (26). Nanomedicine is the medical application of nanotechnology and it uses nanomaterials which can improve drug delivery to target area, can improve drug solubility, can minimize degradation and increase drug bioavailability, among others (4,36,37). Nanoparticles can be used as PS, they can help deliver PS by conjugation with antibodies, folate, transferrin or antibodies against the transferrin receptor or can be used as energy transducers (1,4). PS can be encapsulated in liposomes to improve tumor-selective accumulation (38), in micelles to resist elimination by the reticuloendothelial system (39,40), but also in gold nanoparticles (41-43), biodegradable polymer-based nanoparticles, quantum dots (18) carbon nanoparticles and silica nanoparticles (4,17,44).

Nanotheranostics is a new medical field which combines the diagnostic and therapeutic capabilities into one nanoplatform (45). Theranostic nanoparticles could have a great impact on cancer management and could make personalized medicine possible (45-49). Nanoparticles used in nanotheranostics could therefore carry both anticancer agents and imaging probes such as MRI contrast agents to tumors or they could simultaneously deliver multiple therapeutic agents such as chemotherapy and PDT (45).

Upconversion nanoparticles (UCNPs) are a new generation of fluorophores which can convert long wavelength radiation, like near infrared (NIR) light into visible radiation or ultraviolet (UV) light through non-linear optical processes (50). NIR light has the advantage that it can penetrate deeper into tissues but it has the disadvantage that it cannot generate cytotoxic singlet oxygen. UCNPs can absorb NIR light and emit visible radiation which can initiate PS activation (18). Chen *et al* developed a UCNP ($NaYF_4$:Yb^{3+}/Er^{3+}/Tm^{3+})-based micelle capable of NIR-controlled combination chemotherapy and PDT and fluorescent imaging for the treatment of neuroendocrine tumors and found that UCNP-based micelle exhibited

Table I. Summary of the studies supporting the efficacy of daylight photodynamic therapy in precancerous skin lesions.

Lesion	Photosensitizer	No. of patients	Study design	Results	Refs.
AK	MAL	100	D-PDT vs. c-PDT	Similar efficacy	(63)
AK	MAL	35	D-PDT vs. c-PDT	Similar efficacy for AK I	(64)
AK	MAL	646	D-PDT vs. c-PDT	D-PDT more effective than c-PDT	(65)
AK	MAL	26	D-PDT vs. c-PDT	Equal prevention against NMSC	(66)
AK	MAL	46	D-PDT vs. c-PDT	Similar long-term efficacy	(67)
AK	BF-200 ALA, MAL	13	BF-200 ALA D-PDT vs. MAL-D-PDT	BF-200 ALA more effective than MAL	(68)
AK	MAL, HAL	13	HAL D-PDT vs. MAL D-PDT	Similar long-term efficacy	(69)
AK	MAL	22	D-PDT vs. ingenol mebutate gel	Similar efficacy	(72)
AC	MAL	2	Case study D-PDT	Efficacious	(98)
AC	MAL	10	D-PDT observational study	Complete response in 5/10 patients after 12 months	(99)

AK, actinic keratosis; AC, actinic cheilitis; BF-200 ALA, nanoemulsion formulation with 10% aminolaevulinic acid hydrochloride; c-PDT, conventional photodynamic therapy; D-PDT, daylight photodynamic therapy; HAL, hexylaminolaevulinate; MAL, methyl aminolevulinate; NMSC, non-melanoma skin cancer.

excellent imaging capabilities, induced a better antitumor efficacy than PDT and chemotherapy alone and could be a promising nanoplatform for neuroendocrine tumor theranostics (45). Other authors also showed that UCNPs ($NaGdF_4$:Yb/Tm) developed as folic acid (FA)-targeted $NaGdF_4$:Yb/Tm@SiO_2@TiO_2 nanocomposites have potential applications in both magnetic resonance imaging (MRI) and NIR-responsive PDT (51).

4. Updates in PDT for the management of actinic keratoses

AK, also known as solar keratoses, are some of the most common skin lesions (8). AKs typically appear on sun-exposed areas in fair skinned individuals and clinically present as erythematous, flat, scaly papules which can range from a few millimetres to a few centimetres in diameter (5,52). Several treatment options are available for AK, including cryosurgery, curettage, laser ablation, diclofenac gels, dermabrasion, imiquimod, 5-fluorouracil and PDT. Surgical excision is recommended when malignant transformation to SCC is suspected (5-8).

ALA-PDT and MAL-PDT have both been licensed for the treatment of AK (strength of recommendation A, quality of evidence I according to the European guidelines for topical PDT, 2013), the typical clearance rate being 89-92% (30). The treatment is more efficacious for face and scalp lesions than for acral lesions (30).

The use of PDT for the treatment of field cancerization has been recently studied by several authors. Field cancerization represents the existence of subclinical lesions adjacent to the clinically apparent lesions. It is now considered that the treatment of AK alone is not sufficient and that the field of cancerization must be targeted (53). Passos *et al* aimed to explore the outcome of PDT treatment using a nanoformulation of ALA (nano-ALA) in patients with field cancerization and to compare the results with those obtained with MAL-PDT. The authors found that the efficacy of nano-ALA-PDT is higher than the efficacy of MAL-PDT in treating field cancerization (54).

In a randomized, double blind, phase III multicentre study published in 2016, the efficacy and safety of BF-200 ALA, a nanoemulsion formulation with 10% aminolaevulinic acid hydrochloride, was compared with placebo in the field-directed treatment of mild-to-moderate actinic keratosis with PDT using the BF-RhodoLED lamp. BF-200 ALA was found superior to placebo with respect to complete clearance rate and complete lesion rate and the authors concluded that field-directed therapy with BF-200 ALA and BF-RhodoLED lamp is effective and well tolerated (55).

PDT was also compared with other treatment methods available for AK and field cancerization. Daylight MAL-PDT was found more cosmetically acceptable and was associated with a superior tolerability profile when compared to ingenol mebutate (56). MAL-PDT and imiquimod 5% cream were found equally effective in preventing the occurrence of new AKs in patients with field cancerization (57). ALA-PDT showed better clinical results than 35% trichloroacetic acid peel in the treatment of patients with field cancerization (58) and microneedling-assisted PDT was found to produce superior cosmetic results for improving photoaged skin as compared to MAL-PDT (59).

Daylight PDT (D-PDT) for AK is still a hot topic (Table I). Even though conventional PDT (c-PDT) showed very good results, the method presents some inconvenience e.g., long incubation period and adverse reactions such as burning, stinging or pain (60). D-PDT uses visible light to activate the PS and is therefore more cost-effective and less time-consuming (60,61). D-PDT is mostly recommended for non-hyperkeratotic lesions located on sun exposed areas like the face and the scalp and light exposure should begin within 30 min of applying the PS. Sunscreen without physical blocking filters is necessary to protect from UV damage (60,62). Several authors compared

the efficacy of D-PDT to that of c-PDT. In a randomized, investigator-blinded, controlled study, adult patients were treated with MAL D-PDT on one side of the face and MAL c-PDT on the other side of the face. After 12 weeks, 70% of the patients treated with D-PDT and 74% of those treated with c-PDT showed complete response. D-PDT was nearly painless and better tolerated than c-PDT (63). Fargnoli *et al* also evaluated the efficacy and tolerability of D-PDT and c-PDT with MAL in patients with AK and found that, after 3 months of treatment, there were no significant differences in complete response rates between the two methods (87% for D-PDT vs. 91% for c-PDT) in patients with grade I AK, D-PDT however being less effective in the treatment of grade II and grade III AK (64). In a retrospective study performed on 406 patients with AK treated with c-PDT and 240 patients with AK treated with D-PDT the authors reported superior efficacy of D-PDT and concluded that D-PDT may be routinely used to treat multiple AKs for aesthetic purposes (65). The safety and efficacy of D-PDT and c-PDT in the prevention of occurrence of new non-melanoma skin cancer in patients with field cancerization was also studied and findings suggest that D-PDT and c-PDT have equal preventive potential (66). Long-term efficacy, safety and tolerability of D-PDT and c-PDT were evaluated in an intra-individual right-left comparison study. At the 3-month follow-up, 80.6% of patients treated with c-PDT and 78% of those treated with D-PDT had complete lesion remission while at the 12-month follow-up 71.8% of patients treated with D-PDT and 73.7% of patients treated with c-PDT had complete remission. Grade II lesions responded better to c-PDT while D-PDT had a better tolerability profile (67).

New PS agents were also studied in an attempt to improve D-PDT. In a double-blind, split face prospective study, 13 patients with 177 AKs were randomized to receive BF-200 ALA or MAL D-PDT. After 3 months, 84.5% of lesions treated with BF-ALA D-PDT and 74.2% of lesions treated with MAL D-PDT cleared (68). After 12 months, BF-200 ALA D-PDT showed better maintained clearance than MAL D-PDT, the authors therefore concluding that BF-200 ALA shows improved efficacy compared with MAL (69). Hexylaminolaevulinate (HAL) is a long-chained ester of ALA which has better skin penetration than MAL. Neittaanmäki *et al* compared the long-term efficacy of D-PDT with 0.2% HAL with that of 16% MAL and concluded that HAL and MAL have similar efficacies and that the use of low doses of HAL could help reduce treatment costs (70).

When compared to other treatment options for AK, D-PDT with MAL showed significantly better results than diclofenac plus hyaluronic acid gel (71) and similar results with ingenol mebutate gel (72). Calcipotriol pre-treatment prior to D-PDT showed improved efficacy as compared to D-PDT alone. Erythema and desquamation, however, are more frequent in patients pre-treated with calcipotriol, patients therefore preferring D-PDT alone (73). Pre-treatment with 5-FU cream, however, was shown to increase the efficacy of D-PDT without significantly increasing erythema and pain (74).

Since D-PDT requires dry and warm weather condition, there is some concern that the availability of D-PDT might be limited by the meteorological conditions. A study performed in Australia showed that D-PDT can be used throughout the year if weather conditions permit (75). Artificial white light LED PDT seems to be an effective, well tolerated alternative (76) and could be performed when D-PDT is not available.

Some authors aimed at identifying diagnostic techniques which could help assess the efficacy of D-PDT (77-79). Seyed Jafari *et al* used reflectance confocal microscopy (RCM) to evaluate AK lesions before and after D-PDT and found that RCM features of AK correlate with the results of the clinical evaluation and could therefore be used to monitor the efficacy of D-PDT (78). de Souza *et al* measured PpIX fluorescence, STAT3 cross-linking and keratinocyte damage in the skin of nude mice exposed to daylight and low-light PDT. The researchers found a strong correlation between PpIX-weighted light dose and STAT3 cross-linking and between PpIX-weighted light dose and keratinocyte damage (79).

5. Updates in PDT for Bowen's disease and erythroplasia of Queyrat

Bowen's disease (BD) is SCC *in situ* of the skin. Erythroplasia of Queyrat (EQ) is SCC of the mucous membranes (5,52). BD most often affects men and women older than 60 years and is generally located on sun exposed areas. It clinically presents as an erythematous, well-demarcated scaly patch or plaque with irregular borders. Rarely, the lesions may be pigmented. Sun exposure, ionizing radiation, immunosuppression and HPV infection are the most important risk factors for developing BD (5,7,80-83). EQ most often affects uncircumcised men between the ages of 30 and 60 years (5). Clinically, it presents as a well demarcated, shiny, velvety erythematous plaque typically located on the penis, vulva, perianal area or mouth (50). Poor hygiene, local trauma, lack of circumcision and HPV infection are the most important risk factors for developing EQ (5). The treatment options available for BD and EQ are surgical excision, Mohs micrographic surgery, curettage, electrodessication, laser ablation, cryosurgery, topical 5-FU and PDT (5,52).

PDT is very efficient for the treatment of BD (strength of recommendation A, quality of evidence I) according to the European guideline for topical PDT (30), MAL-PDT being associated with 86-93% clearance of lesions.

Previous studies showed that ALA-PDT can be used in combination with surgery, imiquimod and radiotherapy for the treatment of BD with very good results (84,85). Ablative Carbon Dioxide (CO_2) Fractional Laser pre-treatment and erbium:yttrium-aluminium-garnet ablative fractional laser (Er:YAG AFL) were also used in combination with PDT for treating BD. Kim *et al* found that 50% of lesions pre-treated with ablative CO_2 fractional laser completely responded to three PDT sessions and that after four sessions, 90% of the lesions completely cleared (86). Similar results were reported by other authors (87). Ko *et al* compared the recurrence rate, cosmetic outcomes and safety of MAL-PDT to those of Er:YAG AFL-assisted MAL-PDT (Er:YAG AFL-PDT) in 21 patients with 58 BD lesions. The authors found that Er:YAG AFL-PDT was significantly more effective than MAL-PDT, it showed lower recurrence rate and had similar cosmetic outcomes (88).

Even though there is sufficient evidence supporting the effectiveness of topical PDT for the treatment of BD, some authors showed that large BD, with more than 10 cm in diam-

eter, might not be suitable candidates for this method. The authors therefore suggest that a cut-off value of size must be established (89).

PDT also showed promising results for the treatment of EQ (90). Studies therefore showed that 62.5% of patients treated with MAL-PDT and 58.3% of patients treated with ALA-PDT achieved complete remission (91).

6. Updates in PDT in the treatment of other precancerous skin lesions: Actinic cheilitis and keratoacanthoma

Actinic cheilitis (AC) is a premalignant keratosis of the lip (6) most often affecting fair-skinned people who are exposed to UV radiation (7). It is often considered a form of AK located on the lips (5). In the early stages the disease presents as erythematous, scaly papules or plaques with fissures and sometimes erosions affecting the lower lip. In more advanced stages patients present grey-white plaques and sometimes warty nodules (5,6). Several treatment options are available, including vermilionectomy, 5-FU, diclofenac gel, laser ablation, PDT and trichloroacetic acid (6).

A systematic review published in 2015, which included 15 case series with 242 patients, found that 62% of patients treated with PDT for AC showed complete remission at final follow-up and that 47% of the patients evaluated for histological outcome showed histological cure at final follow-up. The authors therefore concluded that PDT has the potential to clinically and histologically treat AC (92).

ALA-patch PDT was also tried in the treatment of AC. The patch has the advantage of standardized delivery of ALA. A study performed on 11 patients with 15 AC lesions reported complete remission in 8 of 11 patients and 12 of 15 lesions at the 3-months follow-up. After 1 year, 10 of 15 lesions showed complete clinical cure, the cosmetic result being excellent (93).

Since some studies found that PDT is not an efficacious treatment for AC (94,95), some authors aimed at finding new methods to improve this technique. Fontes *et al* evaluated the efficacy of MAL-PDT with previous application of CO_2 laser in eight patients with AC of the lower lip. CO_2 laser has the advantage that it allows a better distribution and absorption of the PS. The authors reported clinical improvement in all patients and histopathological improvement of the epithelial dysplasia in 66.6% of patients (96). Other authors compared the efficacy of Er:YAG AFL MAL-PDT with that of two sessions of standard MAL-PDT in 33 patients with histologically confirmed AC. At the 3-month follow-up, the authors found a complete response rate in 92% of patients receiving Er:YAG AFL MAL-PDT and 59% of patients receiving MAL-PDT. After 12 months, 85% of patients treated with Er:YAG AFL MAL-PDT and 29% of those treated with MAL-PDT had complete response rate. The authors concluded that pre-treatment with ablative fractional laser brings significant benefit to PDT for AC (97).

Some good results were found with D-PDT for the treatment of AC (98,99). Fai *et al* treated 10 patients with refractory AC of the lower lip with D-PDT with MAL and obtained complete response in seven patients at 3 months after therapy and five patients at 6-12 months after therapy (99).

Keratoacanthoma is considered by some authors a variant of SCC and by other authors a benign tumor (7). It is characterized by rapid growth and a tendency towards spontaneous regression (5). It typically appears on sun exposed regions. Several variants have been described, including solitary keratoacanthoma, multiple keratoacanthomas, giant keratoacanthoma, keratoacanthoma centrifugum marginatum, generalized eruptive keratoacanthomas of Grzbowski and multiple keratoacanthomas of the Ferguson-Smith type (5). Numerous treatment options are available for keratoacanthoma, including PDT. The data regarding the use of PDT for keratoacanthomas is however scarce and limited to case presentations or case series. While some authors show that PDT could be a good alternative for patients with keratoacanthomas (100,101), other authors suggest that keratoacanthomas could develop after PDT (102,103). Further research is therefore mandatory to support the usefulness of PDT for the treatment of keratoacanthomas.

7. Updates in PDT for lichen sclerosus - a dermatosis with potential for malignant transformation

Lichen sclerosus (LS) is a chronic, inflammatory disease which can affect both anogenital and extragenital regions (7). Genital LS appears in women as white, atrophic, pruritic lesions on the vulva, labia minora, clitoris and introitus and in men as white, atrophic patches, usually non-pruritic, on the prepuce (52). Genital LS is not intrinsically a precancerous condition, but it is associated with chronic scarring which promotes carcinogenesis (7). Halonen *et al* studied the risk of cancer of female patients with genital LS on data from the Finnish Cancer Registry and found that LS is associated with an increased risk of vulvar and vaginal cancer (104). Various treatment options are available for genital LS, including topical glucocorticosteroids, topical calcineurin inhibitors, systemic glucocorticosteroids, oral retinoids, methotrexate and phototherapy, among others (105). Circumcision is a good therapeutic option for male genital lichen sclerosus. According to the Evidence-based (S3) Guideline on (anogenital) Lichen sclerosus published in 2015, PDT can be considered for the treatment of vulvar LS if standard treatment has failed (105).

Shi *et al* compared the effectiveness and adverse reactions of clobetasol propionate, the conventional treatment of vulvar LS, with those of ALA-PDT, in 40 patients with vulvar LS. The authors found that ALA-PDT was associated with a higher complete response rate and longer remission duration than clobetasol propionate and concluded that ALA-PDT is a well-tolerated treatment option for vulvar LS (106).

The effectiveness and safety of PDT for the treatment of vulvar LS were studied by several authors. In a study performed on ten patients with refractory vulvar LS, nine out of ten patients reported improved clinical response and complete disappearance of itching and one patient reported decrease of itching from severe to mild. Side effects were pain, swelling and erythema and were tolerable (107). Another study performed on 102 patients with vulvar LS treated with ALA-PDT weekly for ten weeks found complete and partial response in 87.25% of patients, the greatest response being observed in the reduction of subepithelial ecchymoses and telangiectasia (108). Olejek *et al* also reported significant attenuation in intensity of symptoms in patients treated with ALA-PDT for LS with or without concomitant autoimmune

disease. The level of antinuclear antibodies also significantly decreased, the authors therefore concluding that PDT might also influence the immune status of the patients (109). MAL-PDT was also used in the treatment of nine patients with genital LS with good results (110).

Considering that procedure-related pain is an important adverse effect which limits the patients' adherence to treatment (111), some authors aimed their research at finding alternatives in order to decrease pain and avoid treatment discontinuation (112,113). Cabete *et al* reported good pain control after using inhaled nitrous oxide/oxygen gas mixture during MAL-PDT for vulvar LS. ALA-PDT with green light was also used in 11 patients with vulvar LS associated with severe itching. The authors reported significant improvement in local status, reduction of pruritus and good treatment tolerance, none of the patients requiring treatment cessation or topical analgesics (112).

Since circumcision is an effective therapeutic option for penile LS, the data regarding the usefulness of PDT for this condition in men is scarce. In a recent study, however, Mercuri *et al* showed that a combination of 1927 nm thulium fiber laser and MAL-PDT was effective in two patients with recalcitrant LS of the penis (114). Further research is however required to establish real effectiveness.

8. Discussion

PDT is a modern therapeutic method which has captured the interest of several authors in recent years. The advances in the development and use of PSs and drug delivery systems are remarkable. With regard to PDT for the treatment of precancerous skin lesions, several authors focused their research on assessing the effectiveness of D-PDT and identifying methods of decreasing technique-related pain. Since data available so far indicate that PDT is a promising treatment in several medical fields, it is expected that further research will be performed in order to improve the efficacy of the technique.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

MT, MIS and CM were responsible for writing the manuscript, editing, acquisition, analysis and interpretation of the data. CIM and MIM contributed to data acquisition, software assistance and editing references. CoC, CaC, MN and SRG contributed to the conception and design of the study and were involved in critical revision of the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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