Dermatology Practical & Conceptual

Photodynamic Therapy for Field Cancerization in the Skin: Where Do We Stand?

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ABSTRACT

Introduction: Photodynamic therapy (PDT) with a photosensitizer is available for the treatment of multiple actinic keratoses (AKs) in a restricted skin area or, as it is established, for the field-cancerized skin.

Objectives: Our review aims to present the up-to-date literature on skin field cancerization using PDT employing different topical photosensitizers, modified light delivery protocols and combination treatments to obtain excellent efficacy and safety in everyday clinical practice.

Methods: We sought PubMed, MEDLINE, Scopus, OVID, Embase, Science Direct, Cochrane Library, Research Gate and Google Scholar for [(aminolevulinic acid OR aminolevulinate) AND photodynamic therapy] with (field-directed OR field cancerization, (actinic keratosis), and (efficacy OR effectiveness OR pain OR tolerability) for studies published until February 2023.

Results: Advantages of PDT compared to the other field treatments, including imiquimod, 5-fluorouracil, ingenol mebutate gel and diclofenac, reported better cosmetic outcomes and greater patient satisfaction. On the other hand, some drawbacks of field PDT include pain and treatment duration. Alternate illumination methods have also been investigated, including daylight as a light source. Pretreating the affected area may enhance photosensitizer absorption leading to better therapeutic results, while combinational treatments have also been tested. Patients prefer daylight PDT to traditional light sources since it is more well-tolerated and equally effective. Even as a preventive treatment, field PDT yields promising outcomes, especially for high-risk individuals, including organ transplant recipients.

Conclusions: This review provides a thorough display of the field of PDT on cancerized skin, which will facilitate physicians in applying PDT more efficiently and intuitively.

Introduction

The permutation of light and chemical agents for managing disorders has its origins in ancient times when the ancient Egyptians and Indians first utilized psoralen to cure the depigmentation of vitiligo under sun exposure [1,2]. In 1903, Niels Finsen won Nobel Prize in Physiology or Medicine for his achievements in this niche. The same year, Von Tappeiner combined light and organic dye eosin for skin cancer treatment giving this therapy the name "photodynamic action", which was the ancestor of modern photodynamic therapy (PDT) [1].

Since the skin is the body organ exposed to the environment and, thereby, to light, dermatology is an area with a plethora of prospects for PDT application, from acne treatment to skin cancer [3,4]. Skin cancer is generally subgrouped into melanoma skin cancer (MSC) and non-melanoma skin cancer (NMSC). MSCs are highly malignant with metastasis potential but are not indicated of PDT. NMSC is universally the most common variant, with basal cell carcinoma (BCC) accounting for 75%-80% of all cases, followed by squamous cell carcinoma (SCC) [5]. Actinic keratoses (AKs) are considered a precancerous type of cutaneous SCC, with a considerably varying risk of malignant transformation assessed between 0.025%-16%. Male sex, older age, and Fitzpatrick I or II phototype skin are predisposing risk factors for AK formation, mainly in patients with chronic exposure to ultraviolet (UVB) radiation and in areas with extensive sunlight exposure such as the face, the hairless scalp, neck and the dorsal extremities [6].

The concept of field cancerization was first introduced by Slaughter et al in 1953 when they detected histologically atypical cells around oral squamous cell carcinoma [7]. Currently, the term skin field cancerization is applied to the skin area clinically with or adjoining to AK on the ground of photodamaged skin. For the diagnosis, a minimum of two of the following signs should be present: telangiectasia, atrophy, pigmentation disorders, and "sandpaper" texture. It is not yet specified whether a visible AK is required for the definition [8]. Nevertheless, field-directed treatment is highly recommended for patients with extensive AKs in large skin areas. For this purpose, various modalities are available, including surgical excision, cryotherapy, curettage, PDT, and topical agents, such as 5-fluorouracil, imiquimod, ingenol mebutate, and diclofenac [9].

Photodynamic therapy is currently considered an efficient method for AK and field cancerization [3]. Its mode of action relies on visible light that interacts with photosensitizing chemical agents, specifically the 5-aminolevulinic acid ALA and methyl-aminolevulinate MAL. Both prodrugs promote protoporphyrin IX (PpIX) production and induce its accumulation because of cells distorted uptake. The reaction of light and photosensitizing compounds generates active oxygen species, which stimulate the apoptotic process of skin cancer cells [10]. Another novel modality, daylight PDT (DL-PDT), gains ground for treating AKs as more appealing, equally beneficial in many cases, well-tolerated, and convenient. It is irrelevant to light-emitting diode (LED) light compared to conventional PDT (C-PDT) since it entails direct exposure to daylight [11].

Objectives

Given the rapid expansion of PDT and skin cancer in the latest years, reviewing its present application in field cancerization and condensing future research trends would be conducive for healthcare professionals. Building on this concept, we gleaned from the international literature the relevant studies and included any available information that would promote the clinical practice and assist investigators in swiftly grasp the progress trends in the field.

Methods

For this review, we searched the following databases: PubMed, MEDLINE, Scopus, OVID, Embase, Science Direct, Cochrane library, Research Gate and Google Scholar. The search terms were [(aminolevulinic acid OR aminolevulinate) AND photodynamic therapy] with (field-directed OR field cancerization, (actinic keratosis), and (efficacy OR effectiveness OR pain OR tolerability). Studies were included from inception to February 2023. We included randomized clinical trials, prospective studies, and randomized comparison studies involving patients with skin field cancerization that had undergone photodynamic therapy, including MAL-PDT, ALA-PDT, C-PDT, DL-PDT, ablative fractional laser resurfacing (AFXL)-PDT, and MAL-DL-PDT.

Data extraction was performed individually for each intervention. The pertinent information obtained from each study was: the first author; year of publication; type of study; type of PDT intervention; the number of patients; demographics of patients; skin phototype; and treatment outcomes. The search included exclusively English-language academic papers. The reference list of the shortlisted articles has also been examined for supplementary studies. This review paper is based on formerly conducted studies and does not encompass any novel trials with human participants or animals conducted by any of the authors.

The study has been designed, and the results have been described as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

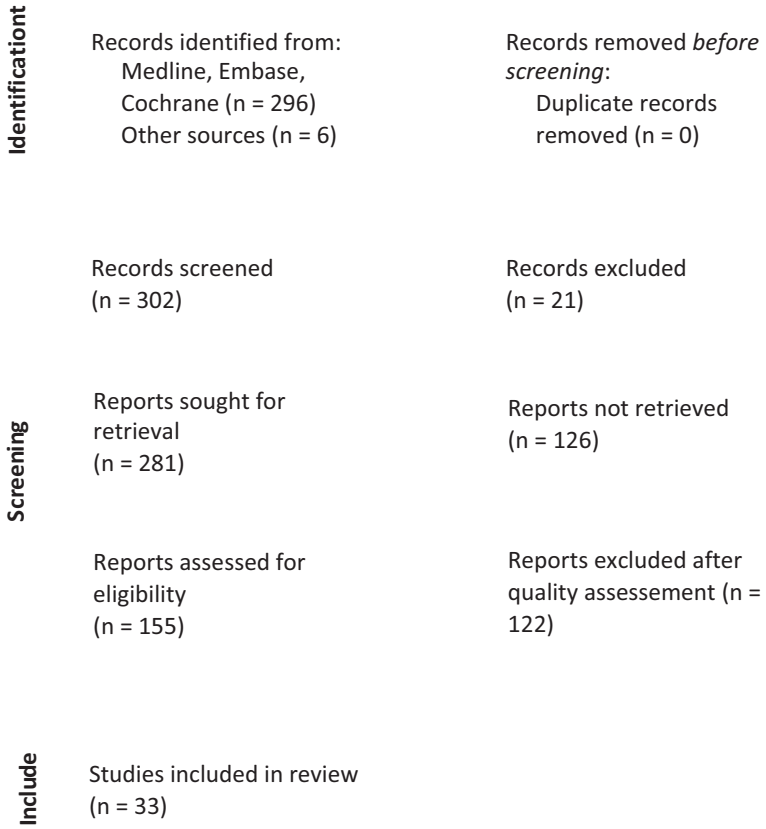

Figure 1. Flow chart of search results and study selection.

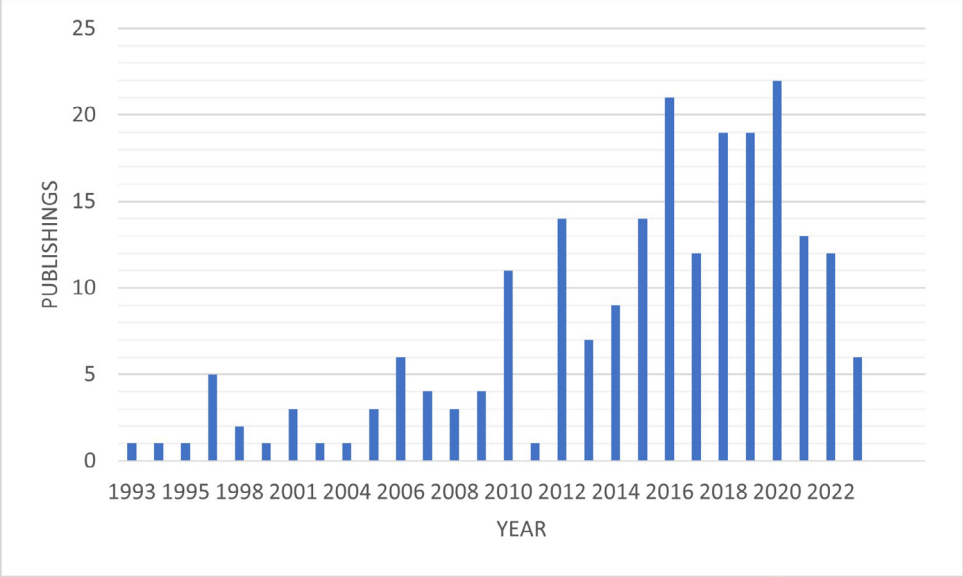

Figure 2. Scientific papers for photodynamic therapy in skin field cancerization published until 2023.

Our literature search yielded 143 studies. After excluding case reports, systematic reviews, duplicate studies, studies that did not present any relevant data or did not conform to the inclusion or exclusion criteria, and studies that referred to individual lesions and not to field cancerized skin and treatment other than photodynamic therapy, we ended up with 33 studies (Figure 1).

Results

The annual timeline analysis illustrates an overall escalating trend in the number of publications, which reveals that PDT on skin field cancerization attracts the increasing interest of the dermatological community (Figure 2). Up to 2023, a total of 193 articles and reviews were linked to PDT in skin

cancer. Skin field cancerization is distinguished by the presence of premalignant and, potentially, cancerous lesions over a limited skin area [9]. In everyday clinical practice, such lesions may not be readily noticeable, or an indication of less extensive and severe lesions could be observed. It has been well documented that sunlight is of key importance for the early development of AK since it promotes mutations in the p53 tumor suppression gene [12]. These mutations are not limited to visible lesions but are also present in sun-exposed skin, where subclinical lesions may occur [13]. Therefore, field-cancerized skin displays identical genetic modifications observed in the malignant lesions. To this extent, treating such lesions is crucial for malignant inhibition, and photodynamic therapy plays a significant role to this end.

In the absence of a robust way to reliably detect subclinical damage of the skin or AKs with potential future malignant transformation, it would be a reasonable approach to treat the entire area of cancerized skin simultaneously with the individual lesions. Surgical treatment is not feasible when an extensive body surface area is involved. On the other hand, topical therapies are often not preferred at some point by patients due to the intense local skin reaction to the drug compound or the lengthy therapeutic course [14]. Under these circumstances, PDT could be considered a complementary or alternative treatment to improve the quality of life and anticipate the undesirable evolvement of the precancerous lesions.

Photodynamic therapy is currently approved for the treatment of AK and field cancerized skin in the U.S.A., Canada, and the European Union, as well as in other countries of the world. The histological improvement in field cancerization after PDT, expressed by less severe and extensive keratinocyte atypia, is a fact, while the remarkable rise of new collagen deposition and the decrease of solar elastosis explain the clinical upgrading of photodamaged skin [15]. Nevertheless, which photosensitizer works best remains inconclusive.

Various randomized controlled trials (RCTs) showed that MAL- and BF-200 ALA-PDT are sufficiently effective in the complete clearance of treated lesions and cosmetic results. However, the use of BF-200 ALA seems to be more well-tolerated for patients. Additionally, it yields superior cosmetic outcomes, is less painful, and has a better overall therapeutic response rate (RR) compared to MAL-PDT [16-21]. After twelve weeks, Dirschka et al showed that BF-200 ALA gel resulted in an almost 20% recurrence rate of AKs in the cancerized field, while the relevant percentage for MAL-PDT was 31.6% [19]. In a similar multicenter study, where authors compared MAL- and BF-200 ALA PDT in grade I-II AK lesions, BF-200 ALA provided a complete clearance (CR) rate of nearly 80% and MAL-PDT a little over 70%. At the same time, it was also proved to be more cost-effective [21]. A phase III multicenter, randomized, double-blind, vehicle-controlled trial examined the efficacy of field-directed treatment with 10% BF-200 ALA gel and red-light PDT in 87 patients with mild-to-moderate AKs of the face and/or scalp. After 12 weeks of the PDT treatment, field-directed PDT obtained complete lesion clearance in 91% of BF-200 ALA-treated patients compared to 22% of vehicle-treated patients [20]. A randomized, double-blind trial compared the efficacy and safety of ALA- and MAL-PDT for the treatment of cancerized skin on the scalp. It concluded that both therapies led to a noteworthy decrease in scalp AKs without one overpowering the other. Nevertheless, the authors noted that ALA-PDT seemed more painful than MAL-PDT in extensive scalp premalignant lesions [22]. One of the earliest trials in the field showed a substantial delay in the onset and a reduction in the number of new lesions when field therapy with ALA-PDT was applied to patients with significant field changes [23]. Relevant results, though, were also reported in another similar study where MAL-PDT was used [24].

When compared to other treatment modalities for skin field cancerization, the lesion-specific clearance for MAL-PDT was significantly higher than other regimens, including ingenol mebutate, diclofenac plus hyaluronate gel, and imiquimod cream. It was also proved that MAL-PDT improved all the traits of chronic photodamage in the dermis underlying and adjacent to the AK lesions [25]. Sotiriou et al. also showed that MAL-PDT provides superior outcomes for the prevention of AK development in patients with field changes after 12 months of follow-up [26]. On the other hand, in a single-blind randomized trial involving four Dutch hospitals, a total of 624 patients with at least five AKs within an area of 25 to 100 cm^2 on the head were recruited and assigned to either MAL-PDT, imiquimod, ingenol mebutate or 5% fluorouracil cream treatment branches. The study concluded that, after 12 months post treatment, 5% fluorouracil cream surpassed the other three field-directed treatments in efficacy [27].

Based on the conventional ALA-PDT, daylight PDT is considered to be more favorable for mild-to-moderate multiple precancerous lesions, demonstrating better patient adherence and moderately low variability in results [28-31]. Although in some cases, for example, when compared to ingenol mebutate, the clearance rates could be fairly inferior, patients still prefer D-PDT due to the almost pain-free sessions and superior cosmetic results [32]. In a large multicenter study including 145 patients with various severity AK grades (I-III), it was found that lesion response rate was notably higher in grade I lesions (75.9%) than in grade II (61.2%) and grade III (49.1%) lesions, whereas most grade II and III AKs (86% and 94%, respectively) were in complete response or downgraded at follow-up [33]. Regarding

the other PDT modalities, Sotiriou et al indicated that, when actinic skin field damage is present, the DL-PDT is the treatment of choice among patients, given the comparable efficacy that it demonstrates when compared to conventional PDT [30]. One of the first studies carried out on this topic was a phase III, randomized, non-inferiority trial throughout Europe including 96 participants with multiple facial or/and scalp AKs. The findings of this study proved that DL-PDT compared with conventional PDT, was equally beneficial, better tolerated and virtually painless, with great patient satisfaction [31]. An intra-individual study including fifty patients from six centers in Germany showed that BF- 200 ALA daylight PDT provided better results than the vehicle regarding the overall lesion clearance rates (86.0% versus 32.9%) to CR (67.3% versus 12.2%) on extremities, trunk, and neck. In the meantime, BF-200 ALA DL-PDT had a lower 12-month total lesion recurrence rate (14.1% versus 27.4%), better cosmetic outcome, and was more well-tolerated [34]. In a single-centre, intraindividual, retrospective study, 19 patients with multiple AKs in the face and scalp received a combination of ALA-PDT and DL-PDT. The results were compared to those of the area that underwent only DL-PDT. The outcomes favoured the combined treatment regarding the clearance rates of AK lesions, whereas the pain was reported to be mild to moderate through red light illumination [35]. In a multicenter, prospective study in Spain, 43 patients with grade I-II AKs on the head initially underwent a session with DL-PDT. After one month of follow-up, participants without a satisfactory therapeutic outcome were randomized either to receive a second session of DL-PDT or to be treated with imiquimod. After one year, clearance rates were higher in the arm of two sessions of DL-PDT monotherapy than that of sequential DL-PDT plus imiquimod (75.2% versus 54.6%, respectively) [36].

The combination of PDT with other treatments, such as cryosurgery, laser application, topical regimens or microneedling, seems to have a synergic action and enhance the therapeutic effect of the respective monotherapy without causing the patients additional discomfort [37-43]. The Microneedle Photodynamic Therapy II trial was a randomized, single-blinded, split-face controlled, 2-arm clinical study where 32 patients with AKs on the face were randomized into two incubations arms, either 10- or 20-minute ALA incubation times, after pretreatment with a microneedle roller or a sham roller. The study results showed that PDT with microneedling pretreatment at a 20-minute ALA incubation time demonstrated equivalent efficacy regarding AK clearance compared to that of a conventional 1-hour ALA incubation time. The further benefit of accelerated treatment was that the procedure was almost painless [37]. In a similar study, Torezan et al combined microneedling or ablative carbon dioxide lasers with MAL-PDT to increase photosensitizer penetration into the skin. The findings favored PDT with microneedling, as it generated superior cosmetic outcomes to conventional MAL-PDT for refining photodamaged skin [38]. Vrani et al used ablative CO_2 fractional laser prior to MAL-PDT treatment with 1-hour incubation in 42 patients with two mirror cancerized areas of the face or scalp and compared it to conventional PDT [43]. After one year of follow-up, the CO_2 fractional laser pretreatment results were equivalent to those of the conventional PDT while allowing for reduced photosensitizer occlusion time, results that were in line with previous studies [43,44]. Pires et al. added acoustic pressure wave ultrasound to the CO2-assisted MAL-PDT with a short incubation time for field cancerization. Overall, 638 AKs in 15 patients were treated either with MAL-PDT alone or with CO2 and acoustic wave ultrasound pretreatment. The efficacy of the novel protocol was reported to be equivalent to the conventional MAL-PDT [42].

A randomized split-scalp study by Torezan et al suggested that topical application of calcipotriol could improve the efficiency of MAL-PDT by 30%, potentially because of the elevated PpIX levels [39]. A bilaterally controlled trial of 17 patients proved that the pretreatment of skin areas with 5-FU for 6 days increased the PpIX levels two- to three-fold nearly after MAL-PDT leading to complete clearance by both enhanced photosensitizer accumulation and induction of p53 [41]. With the application of 5-FU prior to PDT field treatment, the relative clearance rates of MAL-PDT increased from 45% to 75% at 3 months and from 39% to 67% at 6 months, respectively [41]. A study of 58 patients showed that vitamin D3 deficiency could be an aggravating factor regarding the efficacy of PDT, leading to a reduction of effectiveness by nearly 20%. Meanwhile, the administration of high-dose vitamin D3 supplementation (10,000 IU daily for 5 or 14 days) before PDT treatment significantly increased the response rates from 54.4% to 72.5% [40].

A recent study tested the efficacy of three physical pretreatment interventions compared to the standard treatment using daylight PDT. Forty patients were allocated either to standard DL-PDT, DL-PDT with microneedling, DL-PDT with CO2 laser or DL-PDT with microdermabrasion. When DL-PDT was combined with physical methods, it provided better clinical and histologic outcomes. The clearance of AKs was significantly greater 1 and 3 months post treatment with the employment of CO2 laser. Photorejuvenation was more apparent with CO2 laser and microdermabrasion pretreatment. However, only CO2 laser offered a substantial decrease in solar elastosis and an increase in collagen type 1 [45]. Especially when it comes to organ-transplant recipients with resistant to conventional PDT lesions, adding ablative fractional laser along with DL-PDT increases the clearance rates with excellent tolerability than DL-PDT and conventional PDT alone [46]. The regimens mentioned

Table 1. Characteristics of studies and main outcomes.

+First Author/Year of publication	Type of study	Intervention	Number of patients	Time of assessement	Complete Clearance in % (Unless indicated otherwise)
Dirschka et al, 2013	Two prospective randomized controlled phase III trials	MAL-PDT versus BF-200 ALA	482	6 and 12 months	MAL-PDT: 36% and BF- 200 ALA: 47%
Serra-Guillén et al, 2018	Randomized intraindividual comparative	MAL-PDT versus BF-200 ALA	25	1 month	MAL-PDT: 56% and BF- 200 ALA: 62%
Neittaanmäki Perttu et al, 2014	Randomized double-blinded non-sponsored prospective	MAL-PDT versus BF-200 ALA	13	3 months	MALPDT: 74.2% and BF-200 ALA: 84.5%
Dirschka et al, 2018	Randomized intra-individual non-inferiority phase III	DL-MAL-PDT versus BF-200 ALA DL-PDT	52	12 weeks	BF-200 ALA DL-PDT: 79.8% and MAL-DL-PDT: 76.5%
Reinhold et al, 2016	Randomized, double-blind, phase III, multicentre	BF-200 ALA combined with the BF-RhodoLED versus placebo	55 patients received BF-200 ALA, 32 received placebo	3 months with a potential of an additional PDT session	BF-200 ALA: 91% and placebo: 22%
Räsänen et al, 2019	Non-sponsored, prospective randomized double-blind multicentre	BF-200 ALA versus MAL in DL-PDT	69	12 months	BF-200 ALA DL-PDT: 79.7% and MAL DL-PDT: 73.5%
Moloney et al, 2007	Randomized, double-blind, prospective	MAL-PDT versus ALA-PDT	15	1 month	Mean reduction from baseline in AK counts with ALA-PDT: 6.2 +/- 1.9 and MAL-PDT: 5.6 +/- 3.2
Apalla et al, 2010	Randomized placebo-controlled	ALA-PDT versus placebo	39	12 months	ALA-PDT: 64% and placebo: 26%
Kleinpenning et al, 2010	Comparative to baseline	MAL-PDT	14	3 months	42.9%
Arisi et al, 2020	Randomized, cohort	MAL-PDT, ingenol mebutate gel and diclofenac plus hyaluronate gel	90 patients, 30 in each cohort	90 days	MAL-PDT: 23.07%, ingenol mebutate: 30% and diclofenac plus hyaluronate: 14.28%
Sotiriou et al, 2015	Randomized intraindividual comparison	MAL-PDT versus. Imiquimod 5%	44	12 months	No statistically significant difference between the two mirrored fields regarding the development of new lesions.

+First Author/Year of publication	Type of study	Intervention	Number of patients	Time of assessement	Complete Clearance in % (Unless indicated otherwise)
Jansen et al, 2019	Randomized, multicenter	5% fluorouracil, 5% imiquimod, MAL-PDT, or 0.015% ingenol mebutate	624	12 months	Fluorouracil: 74.7%, imiquimod: 53.9%; MAL-PDT: 37.7% and ingenol mebutate: 28.9%
Karrer et al, 2019	Open, interventional, multicenter	MAL DL-PDT	50	3 months	62%
Assikar et al, 2020	Controlled randomized intra-individual	DL-PDT versus PDT	26	3 and 6 months	3 months: DL-PDT: 90.5% and PDT: 94.2%; 6 months: DL-PDT: 90.0% and PDT: 94.6%
Sotiriou et al, 2017	Randomized intra-individual comparative	DL-PDT versus PDT	23	12 months	DL-PDT: 78% and PDT: 80.6%
Lacour et al, 2005	Randomised investigator-blinded controlled phase III	DL-PDT and PDT	108	12 weeks	DL-PDT: 74% and PDT: 70%
Genovese et al, 2016	Intraindividual comparative	DL-PDT versus ingenol mebutate	27	3 months	DL-PDT: 72.4% and ingenol mebutate: 73.6%
Wiegell et al, 2012	Randomized multicenter	MAL DL-PDT	145	3 months	Grade I AKs: 75.9%, grade II: 61.2% and grade III: 49.1%
Ulrich et al, 2021	Vehicle-controlled phase III	BF-200 ALA-PDT versus vehicle	50	12 months	BF-200 ALA-PDT: 86.0% and vehicle: 32.9%
Salido-Vallejo et al, 2020	Single-centre, intraindividual, retrospective	BF-200 ALA-PDT and DL-PDT (combPDT) versus DL-PDT	19	12 weeks	combPDT: 31.6% and DL-PDT: 15.8%
Gracia-Cazaña et al, 2019	Observational, prospective, comparative	DL-PDT versus DL-PDT plus ingenol mebutate	43	12 months	DL-PDT: 75.2% and DL-PDT plus ingenol mebutate: 54.6%
Petukhova et al, 2017	Randomized, single-blinded, split-face controlled, 2-arm clinical trial.	10- or 20-minute ALA incubation times, after pretreatment with a microneedle or sham roller	32	1 month	20-minute incubation arm: microneedle: 76% and sham roller: 58%; 10-minute incubation arm: microneedle: 43% and sham roller: 38%
Torezan et al, 2013	Pilot split-face comparative	Microneedling-PDT versus MAL-PDT	10	1 and 3 months	At day 90, facial erythema ($p = .04$) and coarse wrinkles ($p = .002$) improved on the microneedling-PDT side, compared to MAL-PDT ($p = .01$).

Table 1 (*continued*)

+First Author/Year of publication	Type of study	Intervention	Number of patients	Time of assessement	Complete Clearance in % (Unless indicated otherwise)
Torezan et al, 2018	Randomized split-scalp comparative	Calcipotriol-MAL-PDT versus. MAL-PDT	20	3 months	Calcipotriol-MAL-PDT: 92.1% and MAL-PDT: 82.0%
Bullock et al, 2022	Interventional cohort-controlled	Oral vitamin D3 combined with PDT versus MAL-PDT	29 patients in each group	3 to 6 months	Oral vitamin D3 combined with PDT: 72.5% and MAL-PDT: 54.4%
Maytin et al, 2018	Bilaterally controlled	PDT plus topical 5-fluorouracil versus PDT	17	3, 6, 9, and 12 months	PDT plus topical 5-fluorouracil: 75% and PDT: 45% at 3 months; PDT plus topical 5-fluorouracil: 67% and PDT: 39% at 6 months
Pires et al, 2019	Intra-individual comparative	Acoustic pressure wave ultrasound-CO2-MAL-PDT versus MAL-PDT	15	6 months	Acoustic pressure wave ultrasound-CO2-MAL-PDT: 72% and MAL-PDT: 65%
Vrani et al, 2019	Randomized intraindividual comparison	Fractional CO2 laser-PDT versus PDT	42	12 months	Fractional laser-PDT: 47.2% and PDT: 52.3%
Togsverd-Bo et al, 2012	Randomized comparative	Fractional CO2 laser-PDT versus PDT	15	3 months	Fractional laser-PDT: 88% and PDT: 59%
Bento et al, 2021	Randomized controlled four-arm comparative	DL-PDT; DL-PDT + microneedles; DL-PDT + CO2 laser; DL-PDT + microdermabrasion	40 patients, 10 patients at each group	3 and 6 months	The DL-PDT+ microneedles group had a higher AK-clearance after 1 (p=0,002) and 3 (p=0,034) months. Similar in every group at 6 months (p=0,441)
Togsverd-Bo et al, 2015	Randomized controlled	Ablative fractional laser (AFL)-assisted DL-PDT) (AFL-dPDT) versus DL-PDT), PDT and AFL alone (AFL)	16	3 months	AFL-dPDT: 74%, DL-PDT: 46%, PDT: 50% and AFL: 5%
Togsverd-Bo et al, 2015	Randomized intra-individual controlled	Repeated PDT every 6 months for AK prevention	25	3 years	New AKs in 63% of patients in untreated skin areas versus 28% of patients in PDT-treated skin
Piacquadio et al, 2020	Randomized, parallel-group, evaluator-blinded	ALA 2x versus ALA 3x versus vehicle PDT	166	52 weeks	ALA 2x: 36.0%, ALA 3x: 37.5%, vehicle: 18.9%

ALA = 5-aminolevulinic acid;BF200-ALA = Nanoscale-lipid vesicle formulation with the prodrug 5-aminolevulinic acid;

PDT = photodynamic therapy;

AFXL-PDT = ablative fractional laser resurfacing photodynamic therapy;

DL = daylight photodynamic therapy;

MAL-PDT = methyl aminolevulinate photodynamic therapy.

above appear particularly promising with good tolerance by the patients and could be considered under challenging cases for further promotion in the everyday clinical setting.

An interesting approach is inhibiting the development of precancerous lesions. Building on this concept, PDT might be extended as a prevention tool for skin field cancerization after solid organ transplantation. The relevant clinical study of 25 patients who had undergone kidney transplantation showed that multiple AKs occurred in 63% of the patients; however, only 28% of those patients who received PDT treatment every 6 months for 5 years developed AKs in the face, forearm and hand and the lesions were less extended [47].

Finally, limited data are available regarding the frequency of PDT treatments, especially for the prevention of skin dysplasia. In a 52-week trial, 166 high-risk patients with AKs on the face with prior cryotherapy management and confirmed by biopsy photodamaged but otherwise clinically normal skin were randomized to receive two (baseline and week 4) or three (baseline, week 4, and week 24) sessions of field-directed PDT with broadly applied 20% ALA (or vehicle) to the whole face with a 1-hour incubation time followed by blue light irradiation. At week 52, contrary to the vehicle-PDT arm, patients who underwent three treatments with ALA-PDT developed notably fewer AKs (mean: 2.1 versus 4.7), were more likely to have no AKs (37.5% versus 18.9%), and they demonstrated long-term response (33.3 weeks versus 25.9 weeks). At the same time, fewer new NMSCs occurred in this group. No clinically significant difference in efficacy and safety was observed between two and three ALA-PDT sessions [48].

Conclusions

Several types of PDT are being employed for the treatment of field cancerization with successful results. The clearance of the lesions reaches more than 90%, especially in patients with multiple grade I-II AKs. Advances regarding the illumination delivery systems and photosensitizer modalities have been examined and considered to likely achieve the therapeutic goals (Table 1). However, further studies are needed to establish optimal treatment protocols that would maximize the efficacy and obtain a long-lasting outcome. Finally, yet importantly, the patient experience itself must be at the heart of the discussion, in order to ensure long-standing adherence for a chronic and regressing condition, particularly in individuals at risk.

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