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Photodynamic Therapy in Dermatology: Current Treatments and Implications

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A B S T R A C T

This article provides an update on photodynamic therapy by discussing each of the essential components in sequence: mechanisms of action, common photosensitizers, typical light sources, and indications. In dermatology, photodynamic therapy (PDT) is mainly used in the treatment of superficial skin cancers: actinic keratoses, Bowen's disease and superficial basal cell carcinomas. However, the range of indications has been expanding continuously. PDT is also used for the treatment of other oncological indications and non-malignant conditions such as acne vulgaris and photoaged skin. The 5-aminolevulinic acid (ALA) or its methyl ester (MAL) is applied topically as photosensitizer before activation with visible light. The advantages of topical PDT are: ability to treat multiple lesions simultaneously, low invasiveness, good tolerance and excellent cosmetic results.

***Key words**: photodynamic therapy, superficial skin cancers*

Introduction

Although a relatively novel procedure, photodynamic therapy (PDT) has enjoyed increased importance in the management of skin disease, including therapy and prevention, during last decades. PDT involves the light that actives a photosensitizer resulting in the formation of cytotoxic reactive oxygen species in diseased tissue. The aim is selective destruction of premalignant and malignant cells with the preservation of surrounding normal cells[1–4].

The photosensitizers are systemic and topical. Porfimer sodium (*Photofrin*) is a hematoporphyrin derivate used intravenous[5]. It is rarely used as the photosensitivity remains for several weeks[6]. Second generation of systemic photosensitizers have faster and selective tissue accumulation with shorter half-life[7]. The topically used photosensitizers in dermatology are 5-aminolevulinic acid (5-ALA) and its ethylated ester methyl aminolevulinic acid (MAL). MAL has a more selective accumulation of porphyrin in premalignant and malignant skin cells[1,8–12]; it is more lipophilic and therefore it may penetrate more deeply into lesions and also more rapidly achieves the maximum in intracellular protoporphyrin concentration which leads to a shorter incubation time of three hours compared with ALA[13,14]. Additionally, the usage of liposomal vehicle or nanocolloical ALA preparations might greatly reduce the concentration of ALA with still good penetration and accumulation in tumor cells[13,15]. 5-ALA and MAL itself are not photosensitizers. They are precursors of the intrinsic intracellular heme biosynthetic pathway, which results in the production of photoactive porphyrins[16]. Following application, 5 ALA and MAL are converted into mainly Protoporphyrin IX but also in other intermediate photosensitizing porphyrins that are essential for the transfer of singlet oxygen species and the generation of free radicals. Although PDT results in singlet oxygen species and free radical formation, these species are relatively short lived, with a radius of only 0.01 mm, and thus have low mutagenic potential for nonlocalized DNA damage[8]. Formed singlet oxygen reacts with lipids, proteins and nucleic acids and is essential for tumorsž cell damage[17,18]. Moreover, as the porphyrins are synthesized in mitochondria, the primary damage is in mitochondria[19,20]. Other mechanism such as apoptosis, necrosis and vascular damage are also in-

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volved. Apoptosis is more important molecular mechanism of tumors cell damage than necrosis[17,19-21]. Additionally, inflammatory reaction with histamine and other vasoactiv amines, cytokines are involved[22-27]. Moreover, with systemic PDT there is indirect mechanic with damage of blood vessels and ischemia[28-30].

Light Sources

For optimal photosensitize excitation and tissue penetration the right light source is essential[1,2,7,31–32]. In PDT the wave lights from 400–700 nm are used with absorption peak in 405 nm (blue region of sorest band[5,33–35]. Additionally, there are smaller absorption peaks at 505, 540, 580 and 635 nm. The 635 nm absorption peak in the red region has better tissue penetration[36,37]. And therefore is used in therapy of skin tumors up to 2 to 3-mm depth while blue light can be used in therapy of actinic kurtosis (AK)[4,33].

Light sources for PDT are coherent and incoherent broadband lights.

Lasers as coherent sources are »metal vapor« lasers (copper and gold vapor), dye pumped tunable (argon-dye, neodymium:YAG-dye) lasers and diode lasers. Their advantage is seen in therapy of smaller lesions, in shorter irradiation time, and in the use of monochromatic light[38,39].

Incoherent light sources are fluorescent lamps, light emitting diodes (LED), filtered xenon arc and metal halid light. LED are broadband source convenient for therapy of wider area, bigger and multiple tumors and represents „golden standard«in topical PDT[33].

Indications and potential oncological[5,33,34,40–42] and non-oncological[43–47] indications for PDT are AK, Bowen disease (BD), basal cell carcinoma (BCC), squamous cell carcinoma (SCC), cutaneous T-cell lymphoma (CTCL), Kaposi sarcoma, keratoacanthoma, metastasis carcinoma, extramammary Paget's disease, acne, hirsutism, viral and genital warts, cutaneous leishmaniasis, localized scleroderma, cutaneous sarcoidosis, psoriasis vulgaris, and photorejuvenation.

Contraindications

Contraindications for PDT are porphyria, allergy and photoallergy on photosensitizer[48–51].

The most common and troublesome acute adverse event of topical PDT is the burning and stinging pain that occurs during light exposure, and may continue after exposure. Pain is restricted to the illuminated area and may reflect nerve stimulation and /or tissue damage by ROS, possibly aggravated by hyperthermia[4]. The pain is stronger with larger and ulcerated lesions and lesions on the head[33,34]. According to some studies ALA-PDT is more painful during treatment[52]. The pain may be managed with application of a topical mixture of lignocaine and prilocaine or cold air analgesia[53,54].

The incidence of scarring associated with topical PDT is very low; usually there is good or excellent cosmetic outcome[4].

Postinflammatory hypopigmentation or hyperpigmentation can occur after 48–72 h and increases during the 2 weeks following treatment[55,56].

Hair loss is a potential side-effect of PDT but permanent localized hair loss following PDT is uncommon[57].

PDT treatment-related carcinogenesis is expected to be low or absent compared with UV therapy as PDT does not induce covalent modifications of DNA, formation of ciklobutan pirimidin dimmers[58–60]. Moreover, porphyrin-like molecules also possess antioxidant and antimutagenic properties[60]. Preliminary data using PDT for chemoprevention are promising, with anecdotal evidence suggesting that this therapy may postpone the development of actinic keratoses or nonmelanoma skin cancer[2,31].

Following topical PDT, localized photosensitivity can remain for up to 48 h[61,62].

Indications

AK

The usage of PDT was first approved by FDA for actinic keratoses[2,5]. ALA/ MAL-PDT are highly effective for multiple AK and areas of field cancerization and actinic heilitis[2,63–80]. It can be considered as a first line therapy. It can be used as a single treatment, repeated if necessary after 3 months or even more treatments can be done[1,2]. Complete response rates vary from 50–90% depending on the photosensitizer, number and area of treatment and type of illuminator[2,4,32,69–82]. Higher clearance is seen on the face and scalp, in 71–100%; lesions on acral sites showed lower clearance rates of 44–73% and lower on the lips where more treatment sessions can be applied or a larger area can be treated[1,4,13, 32,83]. Furthermore, it is more effective in thin and moderate thickness AK while hyperkeratotic lesion show lower clearance because of lower penetration of 5-ALA[5]. Blue, green and red light have been used with equal effectiveness[76]. Also there was significant improvement in signs of photoaging[63–68,70,71,73] that might be due to increase of type I collagen seen in intense pulse light activation of ALA and MAL, activation of specific molecular pathways and a nonspecific immune response[2,67,68]. MAL-PDT for AK showed less pain than ALA-PDT with the same light source[76]. Effectiveness of topical PDT and cosmetic outcome following PDT for AK is superior to cryotherapy.

BD

Topical PDT is an effective therapy for BD[32,80,84–96], particularly for large and multiple patch disease and for lesions at unusual sites such as nipple[87], subungual region[88,89] and poor healing sites such as lower leg[90], penis, epidermolysis bullosa[91], radiation dermatitis[92], penis[95] and fingers[93] with equivalence to cryotherapy and equivalence or superiority to topical 5-FU[32,80,94–96]. Further-

more, it can be considered as a first line therapy; the number of treatments were one to three[1,9,32,84–98]; cosmetic outcome is superior to standard cryotherapy and topical 5-FU therapy[84,85,97] (Figures 1 and 2).

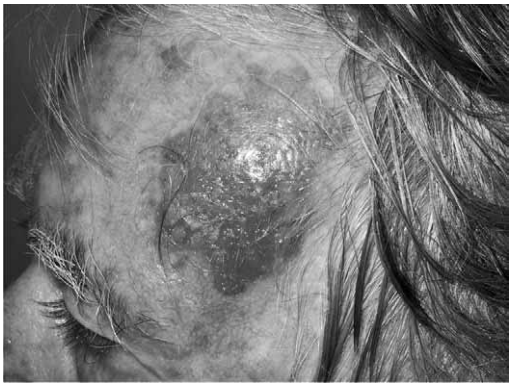

Fig. 1. Bowen's disease (recurrence after surgical excision).

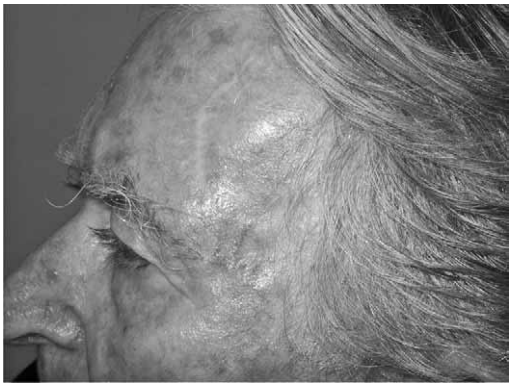

Fig. 2. After one treatment with ALA-PDT (photosenzitizer: 20% 5-ALA, light source: broadband Waldmann PDT 1200 lamp, light dose: 150 J/cm^2).

BCC

The original guidelines from 2002 concluded PDT to be effective in superficial BCC, but that adjunctive therapy might be required to enhance efficacy for nodular BCC[4]. Further approaches taken in an attempt to increase the response of BCC, particularly nodular lesions, have been: the usage of the more lipophilic methyl ester of ALA, MAL; routine usage double PDT treatments; the lesion surface preparation with gentle scraping of superficial lesions, while nodular lesions were prepared by removing intact overlying epidermis with some debulking; usage of fractionation of light[32,99]. Topical MAL–PDT and ALA–PDT are highly effective treatments for superficial BCC[32]. Topical MAL–PDT is effective in nodular BCC, although with a lower efficacy than excision surgery, and may be considered in situations where surgery may be suboptimal[39]. Pigmented and morpheiform basaliomas are resistant to PDT[5]. In comparison with cryotherapy effectiveness of topical PDT and cosmetic outcome following PDT is superior[59] (Figures 3 and 4).

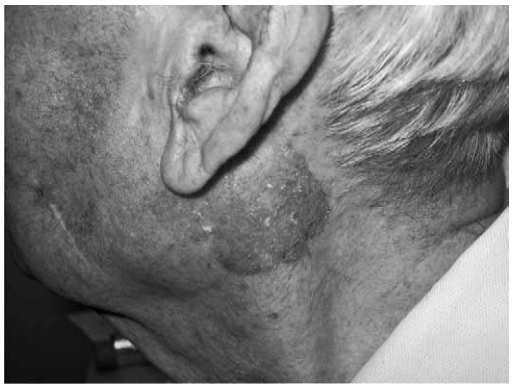

Fig. 3. Superficial basal cell carcinoma (recurrence after surgical excision).

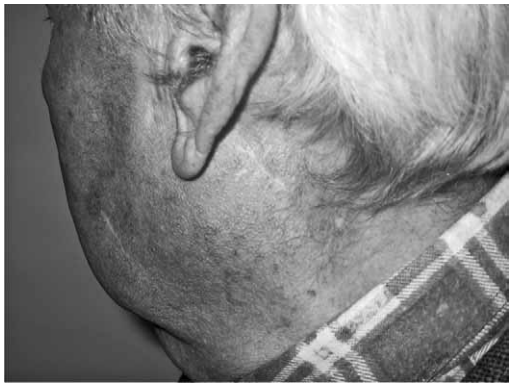

Fig. 4. After two treatments with ALA-PDT (photosenzitizer: 20% 5-ALA, light source: broadband Waldmann PDT 1200 lamp, light dose per session: 150 J/cm^2).

SCC

Current evidence supports the potential usage of topical PDT for superficial, microinvasive SCC limited to papillary dermis, but in view of its metastatic potential, topical PDT cannot currently be recommended for the treatment of invasive SCC with further study required[4,59].

CTCL

The selective uptake of photosensitizers into lymphocytes offers an explanation for the potential usage of PDT in CTCL. Malignant T lymphocytes may be more susceptible than keratinocytes to PDT-induced lysis, as illustrated in a study using the novel photosensitizer silicon phthalocyanine[32,59]. In the limited number of studies performed so far, indications were early stage localized CTCL with multiple treatments usually required for clearance[78]. Further studies of PDT for CTCL are required.

Photodynamic therapy for skin cancer prophylaxis

Current evidence indicates that topical PDT has the potential to provide a preventive role against skin cancer. The potential mechanism is selective destruction of kera-

tinocytes bearing mutated p53 induced by UV exposure or inducing an immune response against neoplastic cells and acting as a biological response modifier[55,56,78].

Photodynamic photorejuvenation

Standard topical PDT and ALA-IPL show the reduction of fine lines and wrinkles, photoaging, telangiectasis, melasma, crow's feet, dyspigmentation, and erythema[63–68].

Acne and related conditions

PDT may promote improvement in acne via antibacterial activity against Propionibacterium acnes, selective damage of sebaceous glands, and reduction in follicular obstruction by keratinocyte shedding and via secondary host responses[78]. Although topical PDT can improve inflammatory acne on the face and back, optimization of protocols, to sustain response while minimizing adverse effects such as induced skin exfoliation and hypepigmentation, is awaited.

Conclusion

ALA or MAL PDT in dermatology is now a well-established treatment option for AK, BD and superficial BCC. In this indications PDT achieves similar clearance rates compared with standard treatment modalities (surgical excision, liquid nitrogen, 5-FU) and shows some important advantages: possibility of simultaneous treatment of multiple and large tumors, relatively short healing times, good patient tolerance and an excellent cosmetic outcome. If result are partial or in case of relapse PDT can be repeated several times until clinical remission occurs because it does not create cumulative toxicity. For other cutaneous malignancies and non-oncological indications, randomized, controlled studies are required which would offer solid evidence of the effectiveness of PDT. In all, PDT appears to be a valuable treatment option in dermatology and dermatologists must continue to strive to make PDT global subspecialty of dermatology.

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FOTODINAMIČKA TERAPIJA U DERMATOLOGIJI: SADAŠNJE PRIMJENE I MOGUĆNOSTI RAZVOJA

S A Ž E T A K

U članku se prikazuju mehanizami djelovanja fotodinamičke terapije (FDT), fotosensitizatori, izvori svjetla i indikacije za FDT. 5-aminolevuliniska kiselina i njezin metilni ester se koriste kao topički fotosenzitizatori. Indikacije za FDT u dermatologiji su prvenstveno površinski tumori kože: aktiničke keratoze, Bowenova bolest i površinski bazocelularni karcinom. Nadalje, indikacije za FDT se stalno nadopunjuju te su proširene i na druge onkološke i neonkološke dijagnoze kao što su vulgarne akne i fotostarenje kože. Prednost FDT terapije je u mogućnsoti liječenja multiplih lezija, niska invazivnost, dobra tolerancija i izvrsni estetski rezultati.