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Topical photodynamic therapy

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ABSTRACT

Topical photodynamic therapy is a therapeutic modality in development, thus arises grate interest among dermatologists worldwide. It is an effective therapy for actinic keratosis, superficial BCC and Bowen's disease. Treatment efficacy, good cosmetics, low risk of skin cancer, low invasiveness, low rate of adverse events, facility for treating multiple or large lesions, especially in poor healing sites and, for penile, digital and facial involvement, low general toxicity and possibility of repeating the treatments with the same efficiency, enable topical photodynamic therapy to become increasingly practiced treatment modality. Researching aimed topical photodynamic therapy to prove as a treatment modality for clinical use in other dermatoses, is in experimental phase. To answer the question when dermatologist should consider using topical photodynamic therapy treatment modatility, we are present available date.

KEY WORDS: *Administration, Topical; Photochemotherapy; Aminolevulinic Acid; Keratosis; Carcinoma, Basal Cell; Carcinoma, Squamous Cell*

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INTRODUCTION

Topical photodynamic therapy (TPT) represents a therapeutic model in progression. Up to now, it has been approved in treatment of actinic keratoses (AK) and basal cell carcinomas (BCC). It is based on the use of photos (Ps) that are activated by visible light and thus produce phototoxic reaction with destruction. It was used for the first time in 1903 for the treatment of skin tumors, condylomata acuminata and tuberculosis of the skin, in combination with eosin and visible light (1). Significant contribution in further development of the TPT was Policard's detection of specific porphyrin accumulation in the tumor tissue, which resulted in terracotta color, each time after systemic administration of hematoporphyrin (2). By an introduction of aminolevulinic acid (ALA) as a local precursor of porphyrin in 1990, contemporary TPT starts with decreased risk of photosensitivity (3). This therapy is effective in the treatment of AK, Bowen's disease and superficial BCC, but insufficiently effective in treating nodular BCC and squamous cell carcinoma (SCC) (4-7). There are some reports in the literature about the trials of TPT in the treatment of viral warts, acne, psoriasis and cutaneous T-cell lymphoma (8-16). This therapy has shown numerous advantages regarding the number, location and size of lesions, multiple treatments, outpatient conditions and cosmetic results (17).

In order to highlight this therapy regarding its indications in dermatology, we decided to make a survey from the current literature.

PHOTOSENSITIZERS

Efficacy of the TPT depends mostly on the quality of the photosensitizer (Ps), regarding its chemical purity, specific binding to the tumor tissue, short time between administration and maximal accumulation in the tissue, short half-life, fast elimination from the normal tissue, maximal absorption of the certain wave length of the light that has been used for the optimal tissue penetration, high singlet oxygen transport, which characterize the quality of TPT (18,19).

Up to now, tumor selectivity of the TPT has been insufficiently described. Increased number and permeability of blood vessels in tumor tissue, insufficient lymphatic drainage and low pH values of the interstitial tissue within the tumor influence the selectivity of the therapy (20). The proper time for the light application depends on the interval from the administration of the Ps to its maximal concentration in the tissue, type of the lesion and the nature of the Ps. The longer interval makes the Ps more suitable for the treatment.

Porphyrins, chlorines, phthalocyanines and porphycenes are the four main groups of the Ps available today.

Porphyrins are the most frequently used Ps, but their systemic administration is insufficient in dermatology, making the long period of photosensitivity that lasts 6 to 10 weeks, due to high accumulation and slow elimination from the skin (17). Systemic photosensitivity has been escaped by the administration of porphyrin precursor, δ-ALA, making the TPT very popular not only for therapy but even for diagnostic purposes in dermatology (3). ALA represents the precursor of the endogenous photosensitizer, protoporphyrin IX (PpIX), and is normally produced from the glycine and succinyl CoA during the biosynthesis of the heme (Figure 1) (3).

Intracellular concentration of PpIX increases after the exogenous administration of ALA since it escapes the cellular "feedback" control. Thus, the proper therapeutic concentration of PpIX has been achieved. As a very potent Ps, PpIX has the maximal absorption for the wavelengths 630-635 nm (21). Since ALA can be metabolized within the 48 hours, there is no risk for the delayed phototoxicity. Hydrophilic feature of ALA makes it easily absorbed to the skin. It is mostly used as a cream (10%-30%), rarely as a solution. There are no avail-

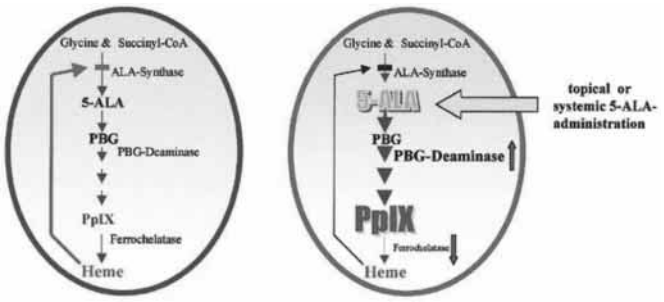


Figure 1. Delta-Aminolevulinic acid - PDT (The haem synthesis pathway)

able dates about its efficacy regarding different formulations . The use of ester-derivates of ALA (methyl-, hexyl- and penthyl- esters) significantly rises because of the increased lipophilicity, which increases the level of PpIX and phototoxicity (21). Thus, many reports about use of methyl-ester of ALA (Metvix®) confirmed the efficacy of TPT in the treatment of AK and BCC with high index of cure (74%- 90%) and excellent cosmetic results (75%-90%) (22-24). Good cosmetic response has also been reported from the numerous double-studied analysis of the efficacy of Metvix-TPT and standard treatment of AK, such as cryotherapy and topical 5-fluorouracil treatment (25,26). However, equally effective Metvix-TPT was more cosmetically acceptable than classical methods.

No consensus has been achieved when the optimal duration of the photosensitizer application has been discussed. It has been shown that duration of application depends on the nature of the disease and Ps applied. In some trials, complete cure has been achieved after the minimal strength of fluorescence. The suggested duration of application intervals range from 3 to 48 hours (7). The duration has been limited to 4-6 hours for the cream (7).

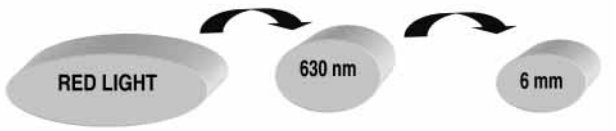
Iontophoresis increases the distribution of ALA and its dosage, though this observation has to be confirmed after clinical trials (27). The penetration of ALA can be increased by dimethyl sulfoxide, deferoxamine, ethylenediamine tetraacetic acid disodium and prior curettage, which is important for the treatment of nodular BCC confirmed by Warloa et al (28). This efficacy for the treatment of non-melanoma skin carcinoma of the skin has been based only on case reports (29,30). When other Ps is discussed, available data are limited (31). Intense studies are going on regarding the topical administration of tetrasodium-meso-tetraphenylporphyrin-sulphonate in the treatment of skin tumors, though limited because of its neurotoxicity.

LIGHT SOURCES AND DOSIMETRY

Successful TPT depends not only on the quality of the Ps but also on the photo activating light within the target tissue. Since the absorption peak of PpIX exists within the visible light, coherent and non-coherent light could be used for the TPT (Table 1) (32).

Table 1. Light sources and dozimetry

Coherent light	Non-coherent light
Argon dye lasers	Xenon arc lamps
Gold vapour lasers	Metal halide lamps
Nd:YAG lasers	LEDs *(light emitting diodes)*
Copper vapour dye lasers	Tungsten/halogen lamps
Semiconductor diode lasers	Fluorescent lamps



The choice of light source depends on the emission-spectrum (in comparison with the PpIX absorption), the total strength of the source, light field, simple usage and financial cost, its advantages towards the other Ps and finally due to the nature of the disease. Many sources have emission within the red light with the wavelength of 630 nm, which penetrates 6 mm in depth (Table 1). Since the light scattering within the skin is high, the therapeutically effective depth is significantly lower and ranges 1-3 mm, which makes the administration of TPT limited to the surface of the lesion (22). Violet, blue and green light penetrate 1-2 mm and are recommended only for the treatment of AK and Bowen's disease.

Optimal therapeutic light dosages are only empiric and are not standardized, being specific for the certain disease. Light dosimetry depends on the size, histopathologic features of the tissue, light source and the nature of Ps. Recently described mathematical model of photodynamic damage showed that low intensity of radiation can be equally effective as the high one when applied during the equal time (33).

After the laser introduction, the indication field for the TPT has been enlarged, especially for the endoscopic procedures. As the sources of the coherent light, lasers provide selective emission, which can be easily adjusted with the absorption spectrum of the Ps. Such sources are not suitable for dermatology since they are too large, non-portable and extremely expensive. More economic polychromatic non-coherent light sources with the white spectrum (400-720 nm) are suitable for dermatology. These observations have been substantiated with the notion that there is no difference in efficacy, between coherent and non-coherent light sources. Modified slide projectors, xenon and halogen lamps are recommended. The fluorescent emission produced by ALA-induced PpIX, can be detected *in vivo* by spectroscopy and fluorescent microscopy. This enables the dynamic detection of Ps distribution in the tissue, making the proper evaluation of the tumor margins easier for the surgeon, during the pre-operative treatment (photodynamic diagnostic - PDD) (3).

PROTOCOL FOR THE TPT IN THE TREATMENT OF NON-MELANOMA SKIN CARCINOMA

The English group responsible for the photodermatology has suggested the Protocol for the safe and effective ALA-TPT, step-by-step (17):

1) Register for each patient with diagnosis (histopathology, photos), number, and size, location of the lesions, associated diseases and therapy, desirable regimen of treatment (duration of photosensitivity, 1 or 2 sessions).

2) Patient Consent form (information about the treatment and signed approval for the treatment)

3) Preradiation treatment: slight curettage, crusts removal with gauze soaped with salt solution with or without pincers and ALA-cream application including 5 mm around the lesion, application of the adherent bandage over the cream (Tegaderm®, 3M®, Loughborough®) plus bandages against visible light (Mepore®, MolnlyckeHealthCare®). ALA-solution must be applied with the cotton applicator also 5 mm around the lesion. After drying, application has to be repeated 3 times with no cover.

4) After 4-6 hours for ALA-cream (after 14-18 hours for ALA-solution), sufficient cream has to be withdrawn, and superficial fluorescence has to be checked by UV Wood-lamp (UVL-56, Upland, CA, U.S.A.)

5) Local anesthetic can be used before the treatment (EMLA® cream - Astra, Kings Langley, U.K.) since sufficient ALA-cream has been previously removed, and 1 hour before radiation (i.e. 3-5 hours), or during the radiation if injection of local anesthetic is used (1%-2% lidocaine).

6) Radiation must be done according to the Protocol specified for each lamp, thus obtaining the irradiation of the margins and the area 5 mm in diameter around the lesion. The optimal position of the light source must be checked during the therapy. The total dosage and intensity of the radiation must be registered.

7) The irradiated site must be protected from any further irradiation including visible light during next 24 to 48 hours.

INDICATIONS

Keratosis actinica

Regarding recent reports, ALA-TPT in 1-2 sessions seems to be the most effective treatment for multiple AK that affects large areas, affecting face or scalp. Single session of ALA-TPT confirms the effectiveness of treatment with a high rate of cure (71%-100%). The effectiveness does not depend on concentration (10%-30%), duration of application (3-6 hours) (34-37).

Blue, violet, green and red light, Levulan® and Metvix® have shown the equal effectiveness (22-25,38). Less effective results were obtained with acral involvement (cure rate 44%) than with face involvement (cure rate 91%) (4,5).

Single session ALA-TPT treatment has shown approximately identical effectiveness in comparison with topical treatment with 5-fluorouracil (5-FU). Thus, in 73% the cure rate has been obtained with ALA-TPT, and in 71% with topical 5-FU (5). In randomized multicentric controlled study on 699 AK, Szeimies et al., compared the effectiveness of methyl-5-aminolevulinic TPT and cryotherapy (25). The followed period was 3 months. The results were almost similar. Complete cure was obtained in 69% of patients treated with TPT and in 75% of patients treated with cryotherapy. Better cosmetic results were obtained with TPT. The effectiveness of treatment was not substantiated by histology in all cases. Calzavara-Pinton has detected persistent disease in clinically cured lesions in 3 from 17 lesions, and relapses in 10% of cases after the 24-36 month-follow up (39).

Bowen's disease

Topical TPT with 20% ALA has widely been used in the treatment of Bowen's disease, thus substantiated by 16 reports (3,26,40,41). The effectiveness was detected in 86% cases with single-session ALA-TPT versus 93% cases with multiple-session ALA-TPT. During the 3-36 months follow up, the recurrence rate ranged from 0%-40% (12% in average).

Laser, tungsten, xenon and LED light sources with irradiation time of 3-6 hours were used. The optimal wavelength for Bowen's disease has not been well defined. The red light (630±15 nm) seems to be more effective than green one (540±15 nm) (42). The violet light (420±15 nm) has shown the same effectiveness (cure rate 90%-100%) as the red light (43). Total doses of irradiation ranged from 60-300 J/cm^2. The effectiveness of TPT in comparison with cryotherapy and 5-FU seems to be equal but less side effects and better cosmetic results were obtained with TPT (44,45). This therapy can be used for the treatment of large and multiple lesions of Bowen's disease, erythroplasia Quairat, as well as in the treatment of the therapy-resistant lesions localized on legs, penis and digital and facial involvement (46,47).

Basal cell carcinoma

BCC represents the malignant disease most frequently treated with TPT. The most frequently used Ps was 20% ALA in combination with 30,5-540 J/cm^2. The therapy was effective and safe with complete cure in 79%-100% cases (3,6,7,17,23,31,44,45). When non-homogenous absorption of ALA and/or its insufficient conversion in PpIX within the tumor cells was detected, the results were less effective (48-50).

Nodular and nodular-ulcerative BCC have less effective therapeutic answer. The complete cure rate was detected in 10%-50% (35,41,49). Better results (cure rate of 77%) were obtained by using previous curettage, multiple treatments or by adding amplifier (30,40,51). Scleroderma-like and pigment BCC show non-homogenous and weak fluorescence, and are not suitable for ALA-TPT (52). Limited therapeutic response of pigment lesions seems to be the consequence of the melanin influence on the light penetration .

Complete cure, good control of recurrent and new tumors, with the excellent cosmetic results was obtained in patients with nevoid BCC syndrome (Gorlin syndrome) when multiple sessions of ALA-TPT were administrated (52).

Comparative analysis between ALA-TPT and cryotherapy has shown the equal therapeutic response (53,54).

Based on the available literature data it can be concluded that TPT can be safe in eradication of superficial, 2 mm in depth BCC. This therapy is less effective for nodular BCC, but the effectiveness rises when previous curettage, amplified penetration and multiple-session treatment were used. Conventional therapeutic procedures such as surgical excision, cryotherapy in combination with electro dissection, radiotherapy, liquid nitrogen, Mohs-micrographic surgery, have better results than TPT due to the longer follow-period (55). Thus, surgical removal is still the standard therapeutic option for BCC, while the alternative TPT treatment is reserved for those who are not suitable for surgical treatment, or for those who were previously treated with radiotherapy. In comparison with surgical treatment, better cosmetic and functional results can be obtained with total ablation or/and diminishing the tumor size with multiple-session TPT. This therapy can detect the occult tumors, and can be useful in defying tumor margins prior to ALA-TPT (3).

Squamous cell carcinoma

Mostly, patients with SCC were treated with 20% ALA topically, with different light doses (30-540 J/cm^2) (3,35,39,50). The 3-47-month long follow-up period has shown the effectiveness of TPT in 54%-100% cases (69% in average), with cure rate up to 69% (24% in average) (39,44,56). TPT was less effective in progressive tumors. Calzavara-Pinton (41) has reported the cure rate of 42% in 11 from 12 superficial SCC, 6-8 hours after ALA application, that were histological substantiated in 83% cases after the 24-36 months (39).

Despite the encouraging results, lots of suspicion remains regarding the therapy of SCC with ALA, due to the high metastatic potential and high recurrence rate. In treatment of progressive SCC, TPT is not the first-choice therapy, but adjuvant modality with diagnostic value (57).

Other indications

Encouraging results were obtained in treatment of actinic cheilitis, condylomata acuminata, keratoacanthoma, lichen sclerosus, scleroderma, epidermodysplasia verruciformis, hirsutismus, vulvar intraepithelial neoplasia, and extramammary Paget's disease with TPT (57). Some less effective attempts were done in treatment of metastatic breast carcinoma and malignant melanoma (3,35). Due to Stender et al. common warts can be more effectively treated with multiple-session ALA-TPT in comparison with cryotherapy and placebo-TPT, with cure rate of 56%-100% (8-10). Especially in children, the only significant limiting factor seems to be pain. Good results can be obtained with simultaneous treatment with topical keratolytics.

Experimental use of TPT in alopecia areata (AA) has started after the observation of hypertrichosis arising in patients with cutaneous porphyria and on the sites of injections of hematoporphyrin-derivates (58). In severe cases of AA, TPT failed to bring expected results (59).

Rossman et al. treated hirsutismus with 20% ALA and 100-200 J/cm^2 of light radiation. The final effect depended on the total dosage of radiation, thus the higher dosages produced hair shedding. It means that TPT can damage hair follicle, but selectively, without damaging neighboring skin. When combined red and blue light, TPT can be effective in the treatment of inflamed and comedogenic, mild and less severe acne (A) (17,57). Though the treatment was done without photosensitizer, the possible mechanism encompasses endogenous porphyrin within propionibacterium acnes. Due to the results obtained after the open control

study on 22 patients with mild acne, the effectiveness of ALA-TPT resulted in decrease in sebum production; decrease in sebaceous glands and clinical presence of A (11). Encouraging results of adjuvant ALA-TPT treatment were obtained by Itoh et al. who demonstrated good effects in some patients with acne after several months (12).

It seems that ALA-TPT in patients with vulgar psoriasis (VP), when administrated 3 times per week gives results comparable with dithranol (13). Multiple-session treatment had better but non-predictable results, limited mostly by pain (15,60). Based on clinical and experimental data available, TPT shows distinct antipsoriatic potential. Direct cytotoxicity against keratinocytes and immunomodulatory effects of TPT can substantially reduce psoriatic lesions (13). However, without optimal regimen current use of TPT in patients with VP is only experimental. Limited factors for clinical trials are variable accumulation of Ps, unpredictable clinical response and pain.

The selective accumulation of Ps in lymphocytes after the TPT as well as inhibition of T-cells raised the possibility of effective treatment for patient suffering from mycosis fungoides (MF). Contrary to the clinical remission obtained in one patient with MF after one session of therapy, repeated sessions of ALA-TPT commenced in 2 patients with plaque form of MF resulted in both clinical and histological remission (16,17). This observation was confirmed by others who reported the cure rate of 50% after single session treatment with ALA-TPT (40). Further studies are needed.

SIDE EFFECTS

Side effects of ALA-TPT were shown in Table 3. Pain, burning, tension and itch, confined to the treated area were most frequently reported. They start at the very beginning of light exposure, increase within the several minutes reaching the stable level through the rest of exposition. They can be result of nerve stimulation and/or tissue damage due to reactive oxygen. For most patients, there is no need for analgesic and anesthetic treatment (35,39). It seems that pain depends on lesions, their nature and localization, as well as the dose and wavelength of light. It has been reported that face and scalp are the most sensitive, psoriatic lesions and common warts most painful, and that the red light produces more pain than green. Comparative studies have shown that ALA-TPT is less painful than cryotherapy but equally painful in comparison with the treatment with 5-FU (5,26,45).

Immediately after illumination, erythematic and mild edema with erosions and crusting are common, but they usually evolve after 2 to 6 weeks (40). Contrary, cryotherapy and 5-FU, ulceration in TPT is extremely rare (26,45). There is no generalized photosensitivity after the topical ALA-TPT since ALA-induced PpIX is almost completely eliminated after the 24 hours. Thus, the risk of phototoxic reactions lasts shortly and can be prevented simply by clothes and bandages (27). Allergy to Ps or its vehicle is possible.

Good cosmetic effect after ALA-TPT is well known. If develops, scarring is rare and can be detected only by histology (54). Temporary hypo- and hyperpigmentations are temporary and disappear after 6 months. Persistent hyperpigmentations were seen after the treatment of hirsutismus (38,46,58). Irreversible alopecia was seen in some cases.

CARCINOGENICITY

TPT has potential genotoxic effect, including induction of cleavage of DNA chains, chromosomal aberration and DNA alkylation (61,62). Since porphyrin molecules have antimutagenic features, ALA-TPT prevents carcinogenicity in experimental mice (62). After the 25 years of studies of TPT in humans, and after 10-year administration of ALA-TPT, there were only 2 reports of tumors that could be direct consequence of this therapy (63,64). Wolf et al. have noticed a malignant melanoma occurring on the sites with AK and superficial SCC previously treated with ALA-TPT (64). Though it might be simple coincidence, inflammation and immunosuppression induced by TPT might trigger clinically invisible malignant melanocytes to progress. Based on recent evidences, the risk for cancer occurrence in association with TPT is very low, but long follow-up period must be taken since the carcinogenesis may have prolonged latent period. In conclusion, ALA-TPT has low incidence of side effects, good cosmetic effects and very low rate of carcinogenicity.

COMBINATION OF TPT WITH OTHER THERAPEUTIC MODALITIES

In order to enhance the therapeutic efficacy, TPT can be combined with other therapeutic modalities. In the clinical oncology, the most valuable combined therapeutic procedure represents the TPT as an adjuvant in surgical resection of solid tumors (21,65).

If TPT starts immediately after surgical resection, all malignant cells in the lesion including malignant contamination could be eradicated. Beside the reduction of the tumor, if radical surgery is not indicated, administration of TPT in the preoperative treatment could help and represent a good way to escape scars and to avoid transplantation of the skin (65).

TPT could be combined with other drugs such as chemotherapeutics (doxorubicin hydrochloride-adriamycin), thus giving the best antitumor effects on experimental animal tumor models (66). The best way for enhancing TPT is heating. Thus, hyperemia on the temperature of 40ºC, during or immediately after illumination has better results than TPT alone (67,68). Hyperthermic temperatures produce structural damage on plasmatic and other membranes and increase destruction produced by previous TPT.

The second interesting combination results in the enhanced effect of TPT by hyperbaric hyperoxia. It is well known that hypoxia within the tumors with low vascularization reduces the production of reactive oxygen and decreases photosensitivity (69).

THE FUTURE OF TPT IN DERMATOLOGY

Based on the recent clinical studies worldwide, TPT is safe and effective way of treating AK on the face and scalp, Bowen's disease and BCC. Other indications are under survey. Distinct features of tumors and normal cells enable TPT to destruct cancer cells with minimal or no damage which is the main advantage of this procedure (70). Moreover, TPT represents the non-invasive method and is suitable for treatment of multiple lesions with special localization (pretibial region, perioral region, apices nasi, ear lobe) in one session. Its very low carcinogenicity, very mild general toxicity and repeat procedures without loss in efficacy as well as good cosmetic results, and relatively low cost (rare side effects) represent other advantages of TPT.

Topical agents such as ALA could be administrated even in non-specialized centers (29). Its combination with sensitizing agents that trigger subcellular structures and are responsible for phototoxicity via separate molecular pathways will enhance the efficacy of TPT. This enhancement is based on the cooperation between a physicist, biochemist and clinician.

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