REVIEW

Photodynamic therapy: a review of the literature and image documentation

Terapia fotodinâmica: revisão da literatura e documentação iconográfica

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Abstract: Photodynamic therapy (PDT) consists of a chemical reaction activated by light energy that is used to selectively destroy tissue. The reaction requires a photosensitizer in the target tissue, a light source and oxygen. The most extensively studied photosensitizing agents for PDT are 5-aminolevulinic acid for the treatment of actinic keratosis and methyl-aminolevulinate, which has been approved for the treatment of actinic keratosis, basal cell carcinoma and Bowen's disease. The light sources used in photodynamic therapy should emit light at wavelengths within the absorption spectrum of the photosensitizer used in PDT treatment. Light emitting diode (LED) lamps are indicated for the photodynamic treatment of non-melanoma skin cancer. PDT should be considered as a therapeutic option, particularly in the case of patients with superficial, multiple or disseminated lesions and for immunosuppressed patients. More recently, PDT has been indicated for a wide range of dermatological conditions such as photo-damaged skin, acne, hidradenitis, scleroderma, psoriasis, warts and leishmaniosis, among others. This article provides an extensive review of photodynamic therapy, its mechanisms, indications and results.
Keywords: 5-aminolevulinate synthetase; Photochemotherapy; Review

Resumo: A terapia fotodinâmica é uma reação química ativada por luz usada para destruição seletiva de um tecido e requer um agente fotossensibilizante no tecido-alvo, uma fonte de luz e oxigênio. Estão disponíveis, no momento, o ácido 5-aminolevulínico para tratamento de ceratoses actínicas e o metilaminolevulinato, aprovado para tratamento de ceratoses actínicas, carcinoma basocelular e doença de Bowen. As fontes de luz utilizadas para a terapia fotodinâmica devem emitir comprimentos de onda no espectro de absorção do fotossensibilizante escolhido. As lâmpadas LED (*light emitting diode*) são as indicadas para terapia fotodinâmica tópica no tratamento do câncer de pele não melanoma. A terapia fotodinâmica deve ser considerada, em particular, para pacientes que apresentam lesões superficiais, múltiplas, disseminadas e para pacientes imunossuprimidos. Mais recentemente, a terapia fotodinâmica tem sido indicada no tratamento do fotoenvelhecimento, acne, hidrosadenite, esclerodermia, psoríase, verrugas, leishmaniose, entre outras. Por este trabalho será possível ter acesso a uma extensa revisão da literatura sobre terapia fotodinâmica, seus mecanismos, indicações e resultados, seguida de comentários e críticas pertinentes ao assunto.
Palavras-chave: 5-aminolevulinato sintetase; Fotoquimioterapia; Revisão

INTRODUCTION

The association of light and chemicals to treat skin diseases is widely used in dermatology. This process is referred to as photochemotherapy and the best example of the technique is the association of psoralen and ultraviolet light (PUVA).[1] Photodynamic therapy (PDT) may be considered a particular form of photochemotherapy that uses a photosensitizer, light and oxygen. Photosensitizers used in this process include 5-aminolevulinic acid (ALA) and its lipophilic derivative, methyl-aminolevulinate (MAL),[2] which is used in the treatment of various malignant tumors. In dermatology, it is indicated for the treatment of non-melanoma skin cancer. More recently, it has been used to treat nonneoplastic dermatoses such as alterations related to photoaging. PDT has proven effective in cases of actinic keratosis (AK) lesions, basal cell carci-

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noma (BCC) and Bowen's disease, since it has the advantage of being able to treat multiple tumors simultaneously. In addition, recovery time is rapid and cosmetic results are excellent. [3]

Background

PDT is defined as a photochemical reaction used to selectively destroy tissue. It is a two-stage therapeutic technique in which the use of a topical or systemic sensitizing drug is followed by visible light radiation. The photosensitizers, administered exogenously or formed endogenously, are activated by the light and transfer energy to molecular oxygen, thereby generating reactive oxygen species to induce cell death. [4,5]

For the treatment of tumors of the gastrointestinal tract, brain tumors or bronchopulmonary tumors, photosensitizers are administered orally or intravenously. For endometrial tumors or bladder carcinoma they are generally administered by instillation, while for the treatment of skin tumors the drugs are effective when applied topically. [2]

History

PDT was first developed at the beginning of the twentieth century in Munich when Oscar Raab and his professor, Herman von Tappeiner, noticed the effects of photosensitivity on paramecia. Raab observed the rapid death of the protozoon *Paramecium caudatum* after light exposure in the presence of acridine dye. The presence of light, which modified the effect of the dye, led to the identification of a photosensitizer. Subsequently, Professor von Tappeiner went on to carry out other experiments and discovered that the presence of oxygen was necessary in order for the reaction to occur, thus creating the term PDT. In 1907, von Tappeiner and Jodlbauer published a textbook on this therapy, which they referred to as an oxygen-dependent photosensitizing process for the treatment of skin tumors and the destruction of infectious particles. They described their experiences with 5% topical eosin and artificial light for the treatment of nonmelanoma skin cancer and for other dermatoses such as lupus vulgaris and condyloma planus. At this time, they speculated that eosin, like acridine, after being incorporated into the cell, would produce a cytotoxic reaction when exposed to an adequate light source in the presence of oxygen. Unfortunately, at that time this important study failed to attract the attention it deserved. [6]

At the beginning of the 1960s, a new drug was synthesized based on the purification of hematoporphyrin (Hp), referred to as a hematoporphyrin derivative (HpD). The prolonged photosensitivity provoked with the use of systemic drugs, the fact that a cure was possible with the use of other more practical methods and the scarcity of publications in the medical literature hindered divulgation of this dermatological technique until 1990. [5] Kennedy et al. [7] proposed a new method using topical ALA as a metabolic precursor of the endogenous photosensitizer, protoporphyrin IX (Pp IX). Pp IX is a potent photosensitizing agent and is degraded during the radiation process with a specific light source. [5]

Photosensitizers in PDT

There was little interest in PDT in dermatology until 1990 when the new technique of topical application of photosensitizers became available. The use of ALA and MAL followed by broad-spectrum red radiation proved to constitute a simple, effective method. Around the same period, some new, second-generation, synthetic sensitizing drugs were developed (derived from benzoporphyrins, phthalocyanines, chlorines and porphycenes). [8]

Some of the ideal characteristics of a photosensitizer include its chemical purity, its ability to target neoplastic tissue, the short interval between administration of the drug and peak accumulation in the tumor, its short half-life, rapid elimination from normal tissue, activation at wavelengths at which penetration in the target tissue is very good, and its ability to produce a large amount of cytotoxic products. [5] In general, lipophilic sensitizing agents are captured by the cell by direct penetration through the plasma membrane, and this uptake increases in direct proportion to the lipophilicity of the drug. The hydrosoluble molecules, however, are captured by pinocytosis. [8] Up to the present time, the mechanisms by which the selective retention of photosensitizers in the malignant tissue occurs remain to be clarified. Some hypotheses include altered permeability of the cell membrane, an increase in the quantity and permeability of blood vessels and reduced lymphatic drainage. In addition, the low pH in the interstitial fluid of the tumors facilitates the selective biodistribution of the photosensitizers. [9]

Systemic photosensitizers

Hp and HpD were the first photosensitizers to be used systemically in clinical studies of PDT. [8] ALA is the first intermediate in the biosynthesis pathway of the heme group, synthesized from glycine and succinate. This reaction is catalyzed by the ALA synthetase enzyme. In the cell cytoplasm, two molecules of ALA form porphobilinogen (PBG) and four molecules of PBG form uroporphyrinogen. This is then converted into coproporphyrinogen and, back inside the mitochondria, into protoporphyrinogen IX. Protoporphyrinogen IX is converted into Pp IX by the effect of

protoporphyrinogen oxidase. Pp IX is a porphyrinic compound with photodynamic activity and emits intense red fluorescence when activated by light. Pp IX may be synthesized locally by all the nucleated cells and is detected in the epidermis within 3-8 hours after systemic administration of ALA. Studies in animals and human volunteers have confirmed that Pp IX is eliminated from the organism between 24 and 48 hours after topical, oral or intravenous administration of ALA. Therefore, the risks of prolonged photosensitivity are minimal.[4]

Topical photosensitizers

In dermatology, PDT with topical ALA has been approved by the US Food and Drug Administration (US FDA) for the treatment of AK since 1999. Furthermore, various studies have reported the successful treatment of acne and photorejuvenation with different protocols, although FDA approval has yet to be issued for these indications.[10] The transport rate of ALA through the plasma membrane is the only limitation to the accumulation of fluorescent porphyrins in the treated cells. This system requires energy, is dependent on the pH and the temperature, and is saturable and slow, being only slightly faster in tumor cells. The best therapeutic results are obtained at concentrations of 10 to 20%.[11]

MAL is an esterified derivative of ALA. It is lipophilic and its selectivity for neoplastic cells is greater than that of ALA. This greater lipophilicity may increase its efficacy in promoting the high levels of phototoxicity induced by Pp IX.[11] MAL is transported by active mechanisms and also by passive diffusion through the membrane. This latter mechanism does not require energy and is not saturable, being effective principally in the neoplastic cells. The greater selectivity for tumor cells, detected by fluorescence of Pp IX, may be increased by its greater penetration through the cell membranes compared to ALA. Soon after penetration, MAL is demethylated to ALA, the subsequent metabolic steps until the production of intramitochondrial Pp IX being the same.[5,8] In Europe, MAL has been approved for the treatment of AK and BCC since 2001. In 2004 it was approved for the treatment of AK in the USA and in 2006 it was approved in Brazil for AK and for superficial and nodular BCC. Currently, MAL has been approved in many countries of Europe, Asia and the Americas for the treatment of AK, BCC and Bowen's disease. Very recently, in 2009, MAL was also approved in Brazil for Bowen's disease. The protocol for the use of PDT with MAL and red light is already well established.

Light sources

Various light sources may be used in topical PDT. Maximum light absorption by porphyrins is close to 405 nm. This range of maximum absorption is referred to as the Soret Band. Other lower peaks of absorption, referred to as Q-bands, are found at 510, 545, 580 and 630 nm. The majority of clinical studies are performed using light wavelengths of 625 to 633 nm, which permit greater skin penetration.[5]

The light sources available for PDT belong to three major groups: broad spectrum lamps, diode lamps and lasers. The non-coherent light sources described in clinical studies on PDT include the halogen lamps used in slide projectors, light-emitting-diode (LED) lamps and, more recently, intense pulsed light (IPL).[12] Currently, the variety of sources emitting non-coherent light is enormous, with a spectrum of light emission that coincides with the absorption peaks of Pp IX.[13] Light with wavelengths of 635 nm is capable of penetrating the skin to a depth of approximately 6 mm compared to 1-2 mm with a wavelength of 400-500 nm. The effective therapeutic depth, nevertheless, appears to be close to 1-3 mm when 635 nm is used. This is due to the capacity to produce a photodynamic reaction, which depends on the dose of light and also on the quantity of photosensitizer used in the target tissue.[14]

Lasers present a specific wavelength that corresponds to the peak absorption of the photosensitizer. Its capacity to emit high flux monochromatic light, associated with its focal precision, allows small lesions to be treated with minimal damage to the surrounding tissue and within a short time interval. Nevertheless, for the treatment of dermatological conditions using PDT and protoporphyrin-based sensitizers, lasers show no advantage over cheaper and more practical equipment options such as non-coherent light sources. These sources emit a large radiation field, enabling larger areas of the skin surface to be treated.[8,13]

Mechanism of action of PDT

PDT involves the administration of a photosensitizing agent into the tissue of a tumor, followed by the activation of this agent using light at a specific wavelength. The treatment consists of two stages. In the first stage, the photosensitizing agent is accumulated, particularly in the tumor cells, following topical or systemic administration. In the second stage, the photosensitized tumor is exposed to light at a wavelength that coincides with the absorption spectrum of the photosensitizing agent. This activated agent transfers energy to molecular oxygen, generating reactive oxygen species (ROS).[1] The subsequent oxidation of the lipids, amino-acids and proteins induces necrosis and apoptosis. In addition, ROS indirectly stimulate the transcription and release of inflammatory mediators.[8]

Oxidation of the cell constituents by ROS dama-

ges the plasma membranes and the cell organelles, with a subsequent alteration in permeability and transport function between the intra- and extracellular media. Inhibition of mitochondrial enzymes appears to represent a key event in cell death by PDT. [14] An apoptotic response to PDT was reported by Agarwal et al. in 1991. [15] This response may be directly induced by PDT without any need for the transduction of intermediary signs that may be lacking in certain drug-resistant neoplastic cells. Cell death by PDT does not appear to depend on the phase of the cell cycle or on genetic factors (e.g. p53 gene).[16]

PDT targets include tumor cells, tissue microvasculature and the host's inflammatory and immune systems. It appears clear that the combination of all these components is required in order to achieve long term control of the tumor. The principal characteristic of the inflammatory process is the release of vasoactive substances, components of the complement, proteinases, peroxidases, cytokines, growth factors and other immuno-regulators. There is evidence of an increase in the regulation of interleukin 1 beta (IL-1beta), interleukin 2 (IL-2), tumor necrosis factor alpha (TNF alpha) and granulocyte colony-stimulating factor (G-CSF). [16]

Application in dermatology

Application technique

Preparing the skin using an adequate technique is fundamental for the success of the treatment. The skin should be cleaned with cotton-wool soaked in a soap-free cleansing lotion, after which alcohol-soaked gauze should be used to wipe the area. The following step consists of superficial debridement of the lesion using a curette. After stopping any bleeding by compression with dry gauze, the selected photosensitizer is applied (Figure 1). ALA, marketed under the brand name of Levulan® in stick form for preparation immediately prior to treatment, and MAL, marketed under the brand name of Metvix® as a ready to use cream, are available on the market in Brazil. The incubation time of the photosensitizer is determined by preestablished protocols. A 1 mm thick layer of MAL cream should be applied over the lesion, leaving a margin of 5-10 mm around it, and maintained for three hours under an occlusive plastic dressing. On top of the plastic dressing, laminating aluminum foil should be applied as protection against the light to avoid any effect of the natural light during the incubation time of the drug (Figure 2). The medication is removed prior to light exposure using dry gauze or saline solution. The time of light exposure and the energy to be used will depend on the light source selected. The MAL-PDT protocol establishes the use of a 635 nm red light with a total dose of 37 J/cm^2. For treatment of AK, a single session of MAL-PDT is indicated; however, a second session may be carried out three months after the first. For the treatment of BCC and Bowen's disease, two sessions are recommended, with an interval of one week between them. The PDT protocols that use ALA vary with respect to the incubation time of the photosensitizer, which may range from 30 minutes to 18 hours, under occlusion or not. Different light sources are used for ALA-PDT. Chemical and physical photoprotection is always recommended following treatment. [12]

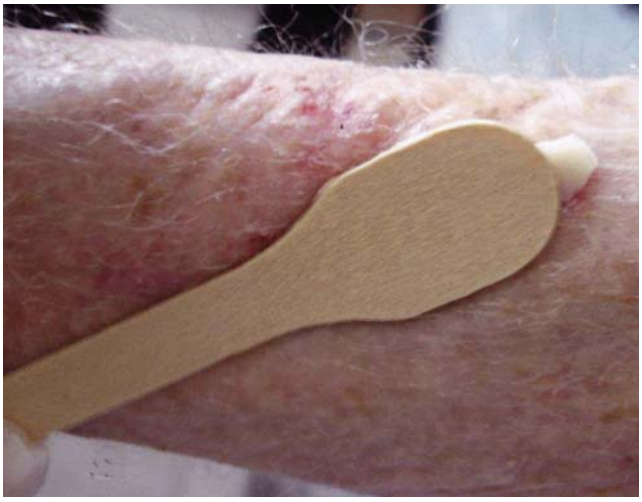

Figure 1: Application of methyl aminolevulinate onto the lesion using a wooden spatula.

Clinical indications

Actinic keratosis

PDT for the treatment of AK was approved by the US regulatory authorities (FDA) in 1999. In general, use of topical PDT for the treatment of AK has a cure rate of 73-100% (Figures 3 and 4). These results are similar to those reported with conventional forms

Figure 2: Occlusion of the photosensitizer using a plastic dressing and aluminum foil to protect it from the light.

of treatment, albeit with fewer side effects and a faster recovery time. [3,17]

ALA associated with blue light has been shown to be effective in the treatment of multiple AK. [18] In initial studies, ALA was left for a period of 14-18 hours of incubation prior to light exposure. More recent studies suggest that an incubation period of less than three hours does not affect the efficacy or safety of the treatment. [19] Other authors have also reported efficacy with an even shorter incubation time that ranged from 30 minutes to one hour for the treatment of AK. [20,21]

Studies with MAL showed greater penetration of this photosensitizer in tumor tissue compared to ALA. [22] A study conducted by Freeman et al. [23] (2003) showed the efficacy of PDT with MAL in the treatment of AK compared to cryotherapy and placebo. MAL-PDT was statistically more effective than placebo-PDT and more effective than more than one cycle of freezing/thawing with liquid nitrogen spray. [23]

Dragieva et al. [24] evaluated the efficacy of PDT with MAL in transplant patients. Complete regression of the 129 lesions or a reduction in their number and size occurred in a maximum period of 16 weeks following the end of treatment. The study concluded that MAL-PDT is safe and effective for the treatment of AK in transplant patients and may reduce the risk of transformation into invasive squamous carcinoma.

Nonmelanoma skin cancer

Basal cell carcinoma (BCC) is the most common malignant skin tumor (70%) in adults and its treatment should be chosen in accordance with the clinical type, size and location of the tumor. Therapeutic options include surgical excision, electrocoagulation and curettage, cryotherapy, immunomodulators, cytotoxic agents and radiotherapy. PDT is a recent therapeutic option for the treatment of nonmelanoma skin cancer and may be considered the treatment of choice in certain cases. Due to the limited light penetration, tumor thickness is a parameter that determines response in PDT and thickness should not exceed 2-3 mm to ensure complete destruction of the lesion. The use of ALA-PDT for BCC has shown poor results. The best result has been described with MAL, possibly due to its greater lipophilicity, greater selectivity and better capacity for penetration. [25]

PDT with MAL and red light has proven effective for these indications, attaining success rates close to 95% in superficial BCC and 73-94% in cases of nodular BCC. The recurrence rate for superficial BCC is approximately 22%, similar to that found with conventional therapies such as cryotherapy, which has a recurrence rate of around 19%. With respect to nodular BCC, however, the recurrence rate is around 14% compared to 4% with surgery, the standard treatment for nodular BCC. These statistical data on MAL-PDT treatment were obtained from multicenter studies with a large number of patients and a follow-up of five years. [3] Many authors have emphasized that the principal advantages of PDT for the treatment of nonmelanoma malignant neoplasias are the significant reduction in recovery time, excellent cosmetic results, the high cure rate and a recurrence rate similar to that reported with other alternatives to surgery. The principal indications include the treatment of multiple lesions, particularly in elderly patients, the treatment of patients for whom surgery is contraindicated and in situations in which the lesions are located in sites that hamper the healing process such as on the lower limbs (Figures 5, 6). In accordance with the guidelines proposed in an international consensus on the use of PDT for the treatment of nonmelanoma skin cancer, MAL-PDT represents an effective option for the

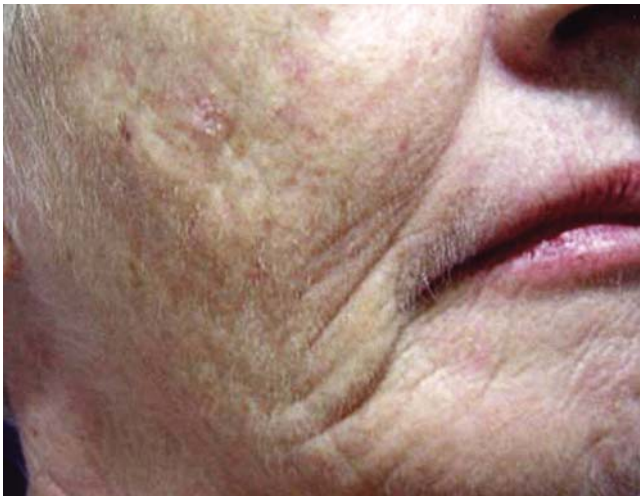

Figure 3: Pretreatment (MAL-PDT) of an area of actinic keratosis on the hemiface.

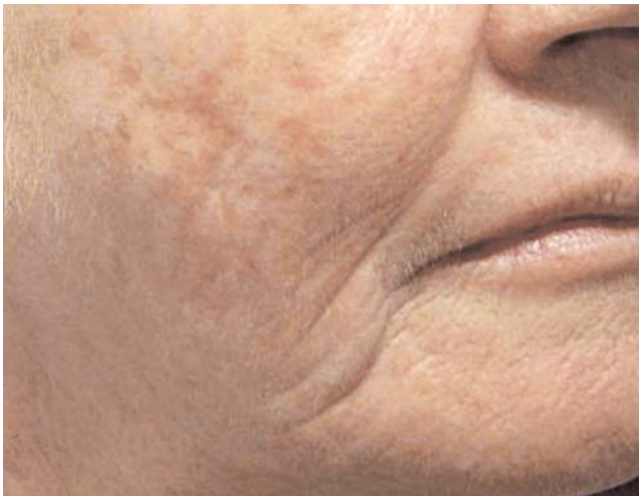

Figure 4: Area of actinic keratosis on the hemiface after three months of treatment (MAL-PDT).

treatment of superficial BCC, principally in the case of large or multiple lesions. Studies on PDT and Bowen's disease describe efficacy as being at least as high as that achieved with cryotherapy and 5-fluorouracil. When correctly indicated, MAL-PDT has shown long-term efficacy in the treatment of nodular BCC over a 5-year follow-up period. [3]

Nonmalignant skin diseases

Acne

The mechanisms of PDT involved in the treatment of acne include the photodestruction of *Propionibacterium acnes*, reduction in the size of the sebaceous glands and a decrease in sebum production. Some authors have also mentioned an effect on the reduction of follicular hypercornification. [26]

Makoto Kimura et al. [27] administered systemic ALA orally at a dose of 10 mg/kg. Four hours after administration the affected area was exposed to visible polychromatic light (close to 630 nm). These authors concluded that oral use of ALA associated with visible polychromatic light is effective for the treatment of body acne. [28]

Some articles mention the use of blue light alone and others compare the greater benefit of ALA in association with this light. The incubation time of ALA varies from study to study, ranging from fifteen minutes to three hours. [29,30,31]

Wichai Hongcharu et al. [32] evaluated patients with back acne both clinically and histologically. The back was divided into four treatment areas. One was treated with ALA 20% and red light, the second with ALA alone and a third with red light alone, while the fourth area was maintained as an untreated control. ALA was occluded for three hours and the light source used had wavelengths of 550-700 nm. Treatment was given once a week for four weeks. The area treated with ALA and red light improved significantly in up to 20 weeks following treatment. Histologically, the sebaceous glands underwent a structural alteration with a reduction in size 20 weeks after PDT. In addition to exfoliation and crusting, the authors reported transitory hyperpigmentation. They concluded that ALA and red light were effective for the treatment of acne vulgaris, causing phototoxicity to the sebaceous follicles with prolonged suppression of sebaceous function. Other studies have confirmed these findings. [33]

The first comparative study in facial acne, using applications of ALA or MAL on each hemiface, was reported in 2006. [34] Both sides of the face were radiated with red light following three hours of use of photosensitizers under an occlusive dressing. Around 75% of the patients treated with ALA and 83% of the patients treated with MAL underwent slight to moderate improvement. The authors suggested that the more significant adverse events on the side of the face to which ALA was applied may have been due to the greater accumulation of Pp IX in the normal skin compared to the side on which MAL was applied.

The use of intense pulsed light (IPL) has also been described as effective for the treatment of acne. The incubation time of ALA may be shorter, a procedure referred to as short contact treatment, for a period of 30 minutes to one hour. [35] PDT with ALA- Pulsed Dye Laser (PDL) may be considered as an alternative to the use of isotretinoin, as the improvement obtained remains for six months. [36]

Photo-damaged skin

Photo-rejuvenation involves the use of a light source (laser or otherwise) to reverse the signs of photo-aging. [37] Recently, new sources have been used successfully in pigment and/or vascular abnormalities

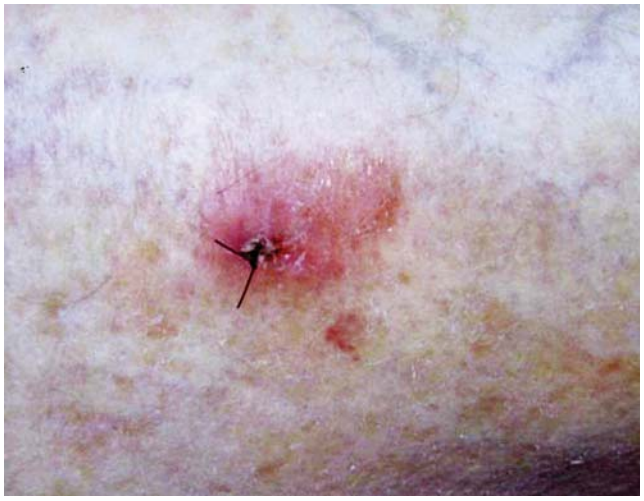

Figure 5: Pretreatment (MAL-PDT) of a superficial basal cell carcinoma lesion on the leg

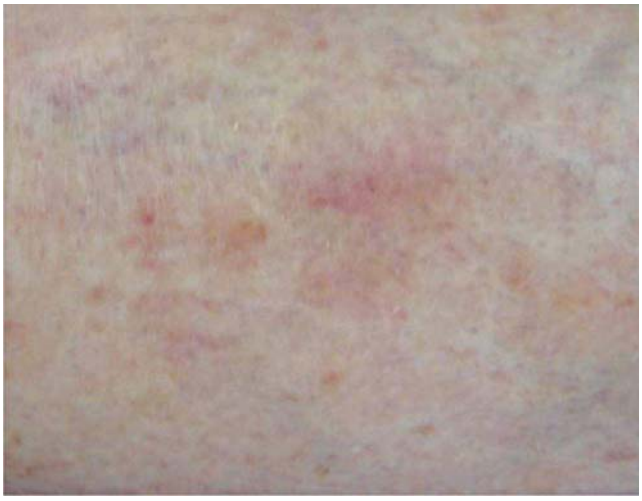

Figure 6: Follow-up of the superficial basal cell carcinoma lesion treated with MAL-PDT after twelve months.

and in inducing collagen synthesis without significantly damaging the epidermis and dermis. These new procedures are better tolerated and result in a faster recovery time for the patient. Examples of these new technologies include intense pulsed light (IPL), pulsed dye laser (PDL), erbium-doped yttrium aluminium garnet laser (ER:Yag), light emitting diodes (LED) and, more recently, PTD using different wavelengths. [38] The light sources used in PDT for rejuvenation include lamps that emit broad spectrum visible light, red light, blue light, argon lasers, PDL and IPL. [39,40]

In the treatment of photo-aging, IPL is able to improve different components of photo-damage except AK. The association of a photosensitizer such as ALA or MAL with an IPL device would therefore be capable of successfully treating all the components of photo-damaged skin. Even when the photosensitizer is used only on the AK lesion, an improvement may also be seen around the lesion. [39] Ruiz-Rodriguez et al. [41] reported on the use of 20% ALA incubated for four hours and IPL (filter of 615 nm) for AK in 17 patients with photo-damaged skin. The patients were submitted to two treatment sessions at a one-month interval. Thirty-three of the 38 AK lesions (91%) were successfully resolved over a three-month follow-up period.

David Avram and Mitchel Goldman [37] reported cure in 68% of cases of AK following a single session of ALA-IPL, associated with an improvement of 55% in telangiectasias, 48% in pigment abnormalities and 25% in rough skin in a follow-up time of three months. Nevertheless, the short follow-up time following treatment of AK with ALA-IPL may lead to a false impression of the safety and efficacy of the method. [41]

The application of ALA-PDT for photo-aging has been widely described in the literature. Zane et al.,[42] however, reported the efficacy and tolerability of MAL in the treatment of photo-damaged skin. These investigators evaluated 20 patients with photo-aging and multiple AK. MAL was applied and maintained under occlusion for three hours prior to exposure to red light at 37 J/cm². Two sessions were carried out with a one-month interval between sessions. There was an improvement in AK, with a cure rate of 88.3% together with an overall improvement in the skin (pigmentation, fine wrinkles and texture). The present findings with MAL (3 hours) and red light are similar to those reported by Zane et al.[42] (Figures 7 and 8). In another study on dermal remodeling of photo-aged skin, in which a 2-hour incubation period of MAL was used, a clinical response was achieved that was similar to that found with three hours of incubation.[43]

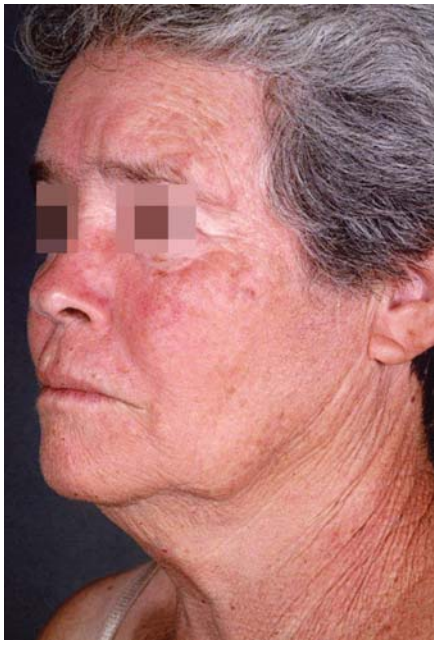

Figure 7: Photo-damaged hemiface, prior to treatment with MAL-PDT

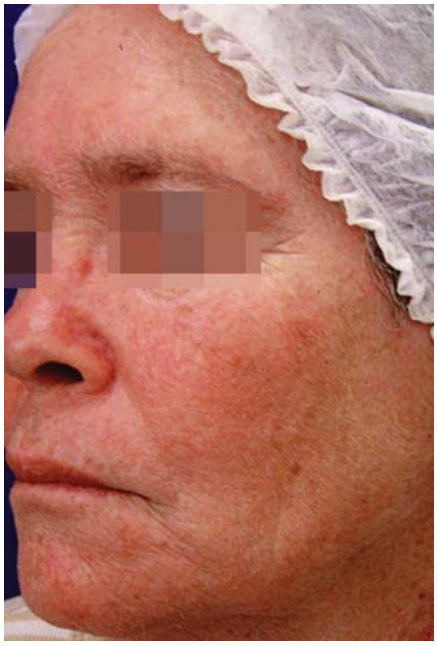

Figure 8: Improvement in photo-damaged skin following six months of treatment with two sessions of MAL-PDT resulting in a "lifting" effect.

Other dermatoses

The indication of PDT for the treatment of other dermatoses is subdivided into categories for the treatment of other neoplasias, inflammatory and immunological diseases, infectious diseases and a group of miscellaneous diseases. These indications include cutaneous lymphoma, viral warts, leishmaniosis, psoriasis, scleroderma, necrobiosis lipoidica and Hailey-Hailey disease.[44-45]

The use of PDT for sebaceous hyperplasia, perioral dermatitis and hidradenitis suppurativa has been reported. PDT with ALA for 45-60 minutes followed by blue light activation has been suggested as an alternative treatment for sebaceous hyperplasias. [46] A study carried out using MAL-PDT in kidney transplant patients with sebaceous hyperplasia confirmed the

safety and efficacy of the treatment.[47]

Herzinger et al.[48] reported the use of 20% ALA and argon PDL in nine patients with genital condyloma and suggested that PDT should not be recommended as first line treatment for this dermatosis. Nevertheless, it may represent an alternative therapy for patients who fail to improve using conventional treatments.

Adverse events

During exposure to light, patients experience a burning or stinging sensation or pruritus, which is restricted to the treated area. The discomfort and pain begins minutes after initiating irradiation, reflecting the nervous stimulus and/or tissue damage caused by the reactive oxygen. Pain, the principal side effect, remains for some hours and decreases over time. With respect to systemic photosensitizers, generalized skin photosensitivity is the principal side effect. ALA may lead to nausea and vomiting in 7-19% of cases and also to transitory changes in liver enzymes. With respect to topical PDT, erythema and edema (Figure 9) may be treated with topical or even systemic corticoids. The normal course includes crusting, desquamation and pruritus of varying intensity for around 2-8 weeks. Photophobia and visual discomfort may occur. Dyschromias are generally reversible within a few months. Blisters, ulcers and necrosis are rare, suggesting a high dose of energy with phototoxicity.[12] In addition, allergic reaction to photosensitizers or to the vehicles should be considered.[5]

Discussion

In general, the use of topical PDT for the treatment of AK results in a high cure rate, similar to that found with conventional treatment with the additional benefits that side effects are fewer and recovery time shorter.[17] The efficacy of MAL-PDT with red light in the treatment of BCC and Bowen's disease has been described in multicenter studies, constituting an excellent option for the treatment of extensive superficial lesions and for patients with multiple lesions. Our evaluation of the treatment of these diseases confirms data published in the literature.

Although the approved indications of PDT are well defined in the international medical literature, little is known on its effect in the so-called "off label" indications. A treatment protocol for non-neoplastic dermatoses has yet to be defined, including proposed variations in skin preparation, in the incubation time of the photosensitizer, in the choice of the different light sources and in the time of light exposure. Many studies refer to PDT as a good option for the treatment of acne, various protocols for the use of ALA or MAL having been reported with success.[34] In our daily practice, we have seen an improvement in inflammatory lesions after two sessions of MAL-PDT, accompanied by intense erythema and edema in the area treated when the incubation period with MAL is longer (2-3 hours). We disagree with other authors who have described PDT as an option that is as effective as the use of oral isotretinoin.

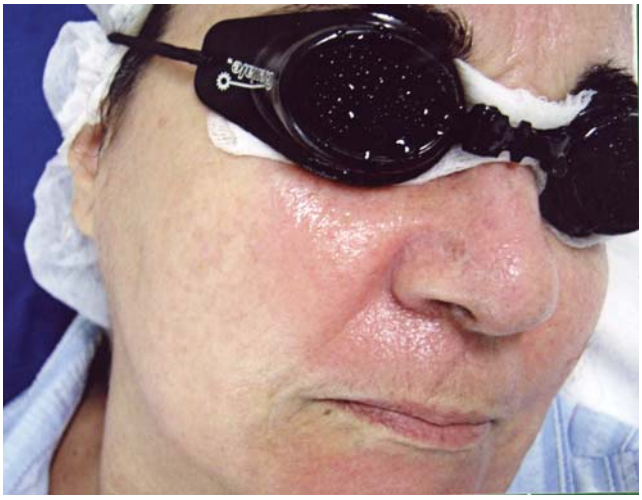

FIGURE 9: Erythema and edema immediately following treatment with MAL-PDT.

Various studies on PDT for photo-damaged skin have reported therapeutic success with this treatment. In these publications, however, the authors refer only to the clinical improvement referred to as photo-rejuvenation.[41]

Very recently, Issa et al. reported a clinical improvement in photo-damaged skin following PDT, confirmed by histopathology and morphometry that showed a significant reduction in elastic fibers after three and six months of treatment, and also a significant increase in collagen fibers after six months of treatment.[49] The authors also discussed possible mechanisms of action of PDT in rejuvenation following an immunohistochemical study in which an increase in metalloproteinases (MMP-9) in the dermis was observed three months after two sessions of MAL-PDT.[50]

Conclusion

Topical PDT using ALA or MAL is approved for the treatment of nonmelanoma skin cancer, the efficacy of his treatment having been confirmed in various studies.[51,52] These substances have different characteristics with respect to their selectivity and ability to penetrate into the skin tumor and for this reason their indications are different.[3] The future path of PDT in oncology treatment should focus on studies on the performance of PDT in chemoprevention. The indication of PDT for patients with multiple AK lesions or for immunosuppressed patients is of particular

importance.[53] No protocol has yet been defined with respect to the number of sessions or the ideal interval between sessions in the chemoprevention of nonmelanoma skin cancer in healthy individuals and in immunosuppressed patients.

With respect to non-oncologic indications, few controlled, randomized studies have been conducted; however, various publications in the literature indicate that PDT is a safe option for the treatment of acne vulgaris, psoriasis, viral warts and localized scleroderma. [54] More recently, it has also been recommended for the treatment of photo-damaged skin. [49,50] We believe that the new indications for PDT in the treatment of the various other non-neoplastic dermatoses should be reserved for specific cases in which PDT could be considered as an alternative therapy rather than a first line option. ❑

REFERÊNCIAS

1. Taylor EL, Brown SB. The advantages of aminolevulinic acid photodynamic Therapy in dermatology. J Dermatolog Treat. 2002;13 Suppl 1:S3-11.
2. Fritsch C, Goerz G, Ruzicka T. Photodynamic therapy in dermatology. Arch Dermatol. 1998;134:207-14.
3. Braathen LR, Szeimies RM, Basset-Seguin N, Bissonnette R, Foley P, Pariser D, et al. Guidelines on the use of photodynamic therapy for nonmelanoma skin cancer: an international consensus. International Society for Photodynamic Therapy in Dermatology, 2005. J Am Acad Dermatol. 2007;56:125-43.
4. Kurwa HA, Barlow RJ. The role of photodynamic therapy in dermatology. Clin Exp Dermatol. 1999;24:143-8.
5. Kalka K, Merk H, Mukhtar H. Photodynamic therapy in dermatology. J Am Acad Dermatol. 2000;42:389-413; quiz 414-6.
6. Taub AF. Photodynamic therapy in dermatology: history and horizons. J Drugs Dermatol. 2004; 3(1 Suppl):S8-25.
7. Kennedy JC, Pottier RH, Pross DC. Photodynamic therapy with Endogenous protoporphyrin IX: basic principles and present clinical experience. J Photochem Photobiol B. 1990;6:143-8.
8. Calzavara-Pinton PG, Venturini M, Sala R. Photodynamic therapy: update 2006. Part 1: Photochemistry and photobiology. J Eur Acad Dermatol Venereol. 2007; 21:293-302.
9. Torezan LAR. Terapia Fotodinâmica em Dermatologia. In: Osório N, Torezan LAR, editors. Laser em Dermatologia. São Paulo: Editora Roca; 2002. p. 121-36.
10. Farah JB, Ralston J, Zeitouni NC. ALA-PDT treatment of pre-skin cancer. In: Goldman MP, editor. Photodynamic Therapy. Philadelphia: Elsevier Saunders; 2005. p. 1-12.
11. Morton CA, Brown SB, Collins S, Ibbotson S, Jenkinson H, Kurwa H, et al. Guidelines for topical photodynamic therapy: report of a workshop of the British Photodermatology Group. Br J Dermatol. 2002;146:552-67.
12. Zelickson BD. Mechanisms of action of topical aminolevulinic acid. In: Goldman MP, editor. Photodynamic Therapy. 1st ed. Philadelphia: Elsevier Saunders; 2005. p. 1-12.
13. Qiang YG, Zhang XP, Li J, Huang Z. Photodynamic therapy for malignant and non-malignant diseases: clinical investigation and application. Chin Med J (Engl). 2006;20;119:845-57.
14. Morton CA. Photodynamic therapy for nonmelanoma skin cancer--and more?Arch Dermatol. 2004;140:116-120.
15. Agarwal ML, Clay ME, Harvey EJ, Evans HH, Antunez AR, Oleinick NL. Photodynamic therapy induces rapid cell death by apoptosis in L5178Y mouse lymphoma cells. Cancer Res. 1991;51:5993-6.
16. Dougherty TJ, Gomer CJ, Henderson BW, Jori G, Kessel D, Korbelik M, et al. Photodynamic therapy. J Natl Cancer Inst. 1998;90:889-905.
17. Goldman M, Atkin D. ALA/PDT in the treatment of actinic keratosis: spot Versus confluent therapy. J Cosmet Laser Ther. 2003;5:107-110.
18. Piacquadio DJ, Chen DM, Farber HF, Fowler JF Jr, Glazer SD, Goodman JJ, et al. Photodynamic therapy with aminolevulinic acid topical solution and visible blue light in the treatment of multiple actinic keratoses of the face and scalp: investigator-blinded,

phase 3, multicenter trials. Arch Dermatol. 2004;140:41-6.
19. Alexiades-Armenakas MR, Geronemus RG. Laser-mediated photodynamic therapy of actinic keratoses. Arch Dermatol. 2003;139:1313-20.
20. Smith S, Piacquadio D, Morhenn V, Atkin D, Fitzpatrick R. Short incubation PDT versus 5-FU in treating actinic keratoses. J Drugs Dermatol. 2003;2:629-35.
21. Touma D, Yaar M, Whitehead S, Konnikov N, Gilchrest BA. A trial of short incubation, broad-area photodynamic therapy for facial actinic keratoses and diffuse photodamage. Arch Dermatol. 2004;140:33-40.
22. Fink-Puches R, Soyer HP, Hofer A, Kerl H, Wolf P. Long-term follow-up and histological changes of superficial nonmelanoma skin cancers treated with topical delta-aminolevulinic acid photodynamic therapy. Arch Dermatol. 1998;134:821-6.
23. Freeman M, Vinciullo C, Francis D, Spelman L, Nguyen R, Fergin P, et al. A comparison of photodynamic therapy using topical methyl aminolevulinate (Metvix) with single cycle cryotherapy in patients with actinic keratosis: a prospective, randomized study. J Dermatolog Treat. 2003;14:99-106.
24. Dragieva G, Prinz BM, Hafner J, Dummer R, Burg G, Binswanger U, et al. A randomized controlled clinical trial of topical photodynamic therapy with methyl aminolaevulinate in the treatment of actinic keratoses in transplant recipients. Br J Dermatol. 2004;151:196-200.
25. Szeimies RM. Methyl aminolevulinate-photodynamic therapy for basal cell carcinoma. Dermatol Clin. 2007;25:89-94.
26. Katsambas A, Dessinioti C. New and emerging treatments in dermatology: acne. Dermatol Ther. 2008;21:86-95.
27. Kimura M, Itoh Y, Tokuoka Y, Kawashima N. Delta-aminolevulinic Acid. Based photodynamic therapy for acne on the body. J Dermatol. 2004;31:956-960.
28. Itoh Y, Ninomiya Y, Tajima S, Ishibashi A. Photodynamic therapy for acne vulgaris with topical 5-aminolevulinic acid. Arch Dermatol. 2000;136:1093-5.
29. Futsaether CM, Kjeldstad B, Johnsson A. Intracellular pH changes induced in Propionibacterium acnes by UVA radiation and blue light. J Photochem Photobiol B. 1995;31:125-31.
30. Taub AF. Photodynamic therapy for the treatment of acne: a pilot study. J Drugs Dermatol. 2004;3(6 Suppl):S10-14.
31. Tzung TY, Wu KH, Huang ML. Blue light phototherapy in the treatment of acne. Photodermatol Photoimmunol Photomed. 2004;20:266-9.
32. Hongcharu W, Taylor CR, Chang Y, Aghassi D, Suthamjariya K, Anderson RR. Topical ALA-photodynamic therapy for the treatment of acne vulgaris. J Invest Dermatol. 2000;115:183-192.
33. Pollock B, Turner D, Stringer MR, Bojar RA, Goulden V, Stables GI, et al. Topical aminolaevulinic acid-photodynamic therapy for the treatment of acne vulgaris: a study of clinical efficacy and mechanism of action. Br J Dermatol. 2004;151:616-22.
34. Wiegell SR, Wulf HC. Photodynamic therapy of acne vulgaris using 5-Aminolevulinic acid versus methyl aminolevulinate. J Am Acad Dermatol. 2006;54:647-51.
35. Gold MH, Bradshaw VL, Boring MM, Bridges TM, Biron JA, Carter LN. The use of a novel intense pulsed light and heat source and ALA-PDT in the treatment of moderate to severe inflammatory acne vulgaris. J Drugs Dermatol. 2004;3(6 Suppl):S15-19.
36. Alexiades-Armenakas M. Long-pulsed dye laser-mediated photodynamic therapy combined with topical therapy for mild to severe comedonal, inflammatory, or cystic acne. J Drugs Dermatol. 2006;5:45-55.
37. Avram DK, Goldman MP. Effectiveness and safety of ALA-IPL in treating actinic keratoses and photodamage. J Drugs Dermatol. 2004;3(1Suppl):S36-9.
38. Nestor MS. Combination therapy in clinical and cosmetic dermatology: the marriage of device and drug. J Drugs Dermatol. 2004;3(5 Suppl):S4-11.
39. Touma DJ, Gilchrest BA. Topical photodynamic therapy: a new tool in cosmetic dermatology. Semin Cutan Med Surg. 2003;22:124-130.
40. Gold MH, Bradshaw VL, Boring MM, Bridges TM, Biron JA. Split-face comparison of photodynamic therapy with 5-aminolevulinic acid and intense pulsed light versus intense pulsed light alone for photodamage. Dermatol Surg. 2006;32:795-801.
41. Ruiz-Rodriguez R, Sanz-Sanchez T, Cordoba S. Photodynamic photorejuvenation. Dermatol Surg. 2002;28:742-4.
42. Zane C, Capezzera R, Sala R, Venturini M, Calzavara-Pinton P. Clinical and echografic analysis of photodynamic therapy using methylaminolevulinate as sensitizer in the treatment of photodamaged facial skin. Lasers Surg Med. 2007;39:203-9.
43. Issa MCA. Estudo da remodelação dérmica induzida pela Terapia Fotodinâmica (MAL-TFD) na pele fotodanificada [Tese]. Rio de Janeiro: Universidade Federal do Rio de Janeiro; 2008.
44. Taub AF. Photodynamic therapy: other uses. Dermatol Clin. 2007;25:101-9.
45. Welch EM, Kelly K. Other Dermatologic indications for ALA-PDT. In: Goldman MP, editor. Photodynamic Therapy. 1st ed. Philadelphia: Elsevier Saunders; 2005. p. 1-12.
46. Richey DR, Hopson B. Treatment of Sebaceous Hyperplasia with Photodynamic Therapy. J Cosmet Dermatol. 2004;17:525-529.
47. Perrett CM, McGregor J, Barlow RJ, Karran P, Proby C, Harwood CA. Topical photodynamic therapy with methyl aminolevulinate to treat sebaceous hyperplasia in an organ transplant recipient. Arch Dermatol. 2006;142:781-782. 111.
48. Herzinger T, Wienecke R, Weisenseel P, Borelli C, Berking C, Degitz K. Photodynamic therapy of genital condylomata in men. Clin Exp Dermatol. 2006;31:51-3.
49. Issa MCA, Piñeiro- Maceira J, Vieira MTC, Olej B, Mandarim-de -Lacerda C, Luiz RR, et al. Photorejuvenation with methyl aminolevulinate and red light: a randomized, prospective, clinical,

histopathologic and morphometric study. Dermatol Surg. 2010;36:39-48.
50. Issa MCA, Piñeiro- Maceira J, Farias RE, Pureza M, Luiz RR, Manela-Azulay M. Immunohistochemical expression of matrix metalloproteinases in photodamaged skin by photodynamic therapy. Br J Dermatol. 2009;161:647-53.
51. Felicio LBA, Ferreira J, Bentley MVB, Bagnato VS, Tedesco AC, Souza CS. A terapia fotodinâmica com ácido 5-aminolevulínico como modalidade de tratamento para neoplasias cutâneas não-melanoma. An Bras Dermatol. 2008;83:309-16.
52. Bakos RM, Babos L, Ferlin E, Cestari T, Orlandini T, Rezende R, et al. Terapêutica fotodinâmica com ácido delta-aminolevulínico em neoplasias queratinocíticas superficiais. An Bras Dermatol. 2003;78:197-207.
53. Gold MH. Photodynamic therapy in dermatology: the next five years. Dermatol Clin. 2007;25:119-20.
54. Torezan L, Niwa ABM, Festa Neto C. Terapia fotodinâmica em dermatologia: princípios básicos e aplicações. An Bras Dermatol. 2009;84:445-5.

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