Aminolevulinic Acid: Actinic Keratosis and Photorejuvenation

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Melanie Palm and Mitchel P. Goldman

Abstract

ALA-PDT is a safe and effective treatment for nonhyperkeratotic lesions. Although FDA-approved for use with a blue light source, other laser and light sources have demonstrated promise in the treatment of actinic keratosis during PDT. Shorter incubation times maintain AK clearance rates but decrease the occurrence of phototoxic adverse events. With careful patient selection, ALA-PDT allows selective field treatment of precancerous skin lesions with improvement in overall photodamage. Patient satisfaction is high and cosmetic results can be excellent.

Aminolevulinic acid (ALA) was the first photosensitizer prodrug to be FDA-approved for use in topical photodynamic therapy (PDT). Since its approval over a decade ago, many aspects of ALA-PDT have been examined. Studies investigating the treatment of nonhyperkeratotic actinic keratosis (AK) with ALA-PDT have led to advances in treatment. Incubation times of ALA have decreased, multiple light sources have been used to elicit the reaction, and cosmetic benefits of treatment have been discovered. In the discussion that follows, background on ALA-PDT is provided. In addition, clinical studies regarding the treatment of AKs and photorejuvenation are summarized. Finally, a practical guide for treatment is provided for the reader to optimize treatment while avoiding common pitfalls of treatment.

Mechanism of PDT

PDT Mechanism of Action

PDT involves the activation of a photosensitizer by light in the presence of an oxygen-rich environment. Topical PDT involves the application of ALA or its methylated derivative (MAL) to the skin for varying periods of time. This leads to the conversion of ALA to protoporphyrin IX (PpIX), an endogenous photactivating agent. PpIX accumulates in rapidly proliferating cells of premalignant and malignant lesions [1], as well as in melanin, blood vessels, and sebaceous glands [2]. Upon activation by a light source and in the presence of oxygen, the sensitizer (PpIX) is oxidized, a process called “photobleaching” [3]. During this process, free radical oxygen singlets are generated, leading to selective destruction of tumor cells by apoptosis without collateral damage to surrounding tissues [4, 5]. Selective destruction of malignant cells is due in part to their reduced ferrochetalase activity, leading to

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excessive accumulation of intracellular PpIX [6]. Recent in vitro research suggests that any remaining malignant cells following PDT have reduced survival [7]. A detailed explanation of the mechanism of action in PDT is found in Chap. 1.

ALA

δ-5-ALA is a hydrophilic, low molecular weight molecule within the heme biosynthesis pathway [1, 8]. ALA is considered a prodrug [9]. In vivo, it is converted to PpIX, a photosensitizer in the PDT reaction. In the United States, ALA is available as a 20% topical solution manufactured under the name Levulan Kerastick (DUSA Pharmaceuticals, Inc., Wilmington, MA). FDA-approved since 1999, Levulan is used for the treatment of nonhyperkeratotic AKs in conjunction with a blue light source, such as the Blu-U (DUSA, Wilmington, MA) [10]. It is supplied as a cardboard tube housing two sealed glass ampules, one containing 354 mg of δ-ALA hydrochloride powder and the other 1.5 mL of solvent [6]. The separate components are mixed within the cardboard sleeve just prior to use.

Esters of ALA are lipophilic derivatives of the parent molecule. Their chemical structure provides increased lipophilicity, allowing superior penetration through cellular lipid bilayers compared to ALA [2, 11]. MAL may offer better tumor selectivity [11–14] and less pain [14, 15] during PDT with less patient discomfort [15] compared to ALA.

Light Irradiation

No standardized guidelines for the "optimal irradiance, wavelength and total dose characteristics for PDT" exist according to the British Dermatology group and the American Society of Photodynamic Therapy Board [9, 16, 17]. However, certain laser and light sources are predictably chosen for PDT activation. Their wavelengths correspond closely with the four absorption peaks along the porphyrin curve. The Soret band (400–410 nm), with a maximal absorption at 405–409 nm, is the highest peak along this curve for photoactivating PpIX. Smaller peaks designated as the "Q bands" exist at approximately 505–510, 540–545, 580–584, and 630–635 nm [1, 2, 8]. There are advantages and disadvantages to exploiting the wavebands in either the Soret or Q bands for PDT. The Soret band peak is 10 to 20-fold larger than the Q bands, and blue light sources are often used to activate PpIX within this portion of the porphyrin curve, targeting lesions up to 2 mm in depth [14]. Longer wavelengths found within the Q bands produce a red light that penetrates more deeply (5 mm into the skin) but necessitates higher energy requirements [1, 8].

Light Sources

Light sources used in PDT can be categorized in a variety of ways, including incoherent versus coherent sources, or by color (and wavelengths) emitted. Incoherent light is emitted as noncollimated light and is provided through broadband lamps, light emitting diodes (LEDs), and intense pulsed light (IPL) systems. Noncoherent light sources are easy to use, affordable, easily obtained, and portable due to their compact size [18]. The earliest uses in PDT were filtered slide projectors that emitted white light [1]. Metal halogen lamps such as the Curelight (Photocure, Oslo, Norway, 570–680 nm) are often employed in PDT as they provide an effective light source in a time, power, and cost-effective manner [1, 19]. In Europe, the PDT 1200 lamp (Waldmann Medizintechnik, VS-Schwennigen, Germany) gained in popularity, providing a unit with high power density emitting a circular field of light radiation from 600 to 800 nm [12, 19]. Short arc, tunable xenon lamps have also been used, emitting light radiation from 400 to 1,200 nm [12]. The only widely available fluorescent lamp used in conjunction with PDT is the Blu-U (DUSA, Wilmington, MA) with a peak emittance at 417 ± 5 nm. LEDs provide a narrower spectrum of light irradiation, usually in a 20–50 nm bandwidth via a compact, solid, but powerful semiconductor [1, 20]. LEDs are simple to operate and are typically small in size, emitting light from the UV to IR portion of the electromagnetic spectrum [20]. However, the diminutive size of most LED panels necessitates multiple rounds of light illumination to treat larger areas. IPL is yet another source of incoherent light, emitting a radiation spectrum from approximately 500 to 1,200 nm [20]. Cutoff filters allow customization of the delivered wavelengths. This light source is particularly useful in photorejuvenation, targeting pigment, blood vessels, and even collagen.

Lasers provide precise doses of light radiation. As collimated light sources, lasers deliver energy to target tissues at specific wavelengths chosen to mimic absorption peaks along the porphyrin curve. Lasers used in PDT include the tunable argon dye laser (blue-green light, 450–530 nm) [12], the copper vapor laser-pumped dye laser (510–578 nm), long-pulse pulsed dye lasers (PDL) (585–595 nm), the Nd:YAG KTP dye laser (532 nm), the gold vapor laser (628 nm), and solid-state diode lasers (630 nm) [19]. Although laser sources allow the physician to delivery light with exact specifications in terms of wavelength and fluence, the fluence rate should be kept in the range of 150–200 mW/cm^2 to avoid hyperthermic effects on tissue [1, 14]. In fact, there is evidence to support that cumulative light dose of greater than 40 J/cm^2 can deplete all available oxygen sources during the oxidation reaction, making higher doses of energy during PDT unnecessary [3].

Clinical Applications

Actinic Keratoses

Background and Epidemiology

Actinic keratoses (AK) are a premalignant skin condition, comprising the third most common reason and 14% of all dermatology office visits [21, 22]. Approximately 4 million Americans are diagnosed with AKs annually [23], and according to one Australian study, 60% of Caucasian Australians aged 40 or older develop this condition [24]. The prevalence of AKs within the US population ranges from 11 to 26% with the highest incidence in southern regions and older Caucasian patients [25].

The concern for untreated AKs is their rate of transformation to cutaneous squamous cell carcinoma (SCC). A small percentage of SCC metastasizes [26], and this is more likely in higher risk areas, such as mucous membranes (e.g., lips) [27]. The reported conversion rate of AK to SCC varies widely, estimated as 0.025–16% per lesion per year [28–32]. AKs may be considered an in situ SCC [33, 34], with AK resting on the precancerous end of a spectrum that leads toward invasive SCC. It has been suggested that the AK/SCC continuum be graded as "cutaneous intraepithelial neoplasia," in a manner analogous to cervical malignancy. Further histopathologic evidence supports the link between AKs and SCC. Both lesions express tumor markers including the tumor suppressor gene p53 [35] and over 90% of biopsied SCCs have adjacent AKs within the examined histopathologic field [36].

Clinical Presentation and Diagnosis

AKs typically appear as 1–3 mm slightly scaly plaques on an erythematous base, often on a background of solar damage. They are often detected more easily through palpation than visual detection [37], due to their hyperkeratotic nature. The surrounding skin often shows signs of moderate to severe photodamage, including dyspigmentation, telangiectasias, and sallow coloration due to solar elastosis (Fig. 2.1). Individual AK lesions may converge, creating larger contiguous lesions. Most AKs are subclincial and not readily apparent to visual or palpable examination. The evidence for subclinical AKs is their fluorescence when exposed to ALA + Wood's lamp or a specialized CCD camera [38].

Although often asymptomatic, AKs may have accompanying burning, pruritus, tenderness, or bleeding [22]. Several variants of AK exist, including nonhyperkeratotic (thin), hyperkeratotic, atrophic, lichenoid, verrucous, horn-like (cutaneous horn), and pigmented variants [25]. AKs on the lip, most often occurring on the lower

Fig. 2.1 Frontal scalp of a 71-year-old white male demonstrating moderate to severe photodamage. Numerous actinic keratoses characterized by erythematous scaly slightly elevated plaques are visible on a background of extensive solar lentigines

lip, are designated as actinic cheilitis [27]. As AKs often result from a long history of UV exposure, the lesions usually arise in heavily sun-exposed areas including the scalp, face, ears, lips, chest, dorsal hands, and extensor forearms [39]. Risk factors for AKs include fair skin (Fitzpatrick skin type I–III), history of extensive, cumulative sun exposure, increasing age, elderly males (due to UV exposure), history or arsenic exposure, and immunosuppression [21, 22].

Histopathology

Histopathologic examination of actinic keratoses is characterized by atypical keratinocytes and architectural disorder [22]. Early lesions demonstrate focal keratinocyte atypia originating at the basal layer of the epidermis and extending variably upward within the epidermis [40]. Hyperchromatic and pleomorphic nuclei and nuclear crowding characterize the cellular findings while architectural disorder is comprised of alternating ortho- and hyperkeratosis, hypogranulosis, and focal areas of downward budding in the basal layer of the epidermis [22, 25]. Solar elastosis is invariably present. Well-developed lesions may have apoptotic cells, mitotic figures, involvement of adnexal structures, lichenoid infiltrates, and a focal tendency toward full-thickness involvement (Fig. 2.2). Full-thickness atypia indicates transformation into SCC-in situ [25].

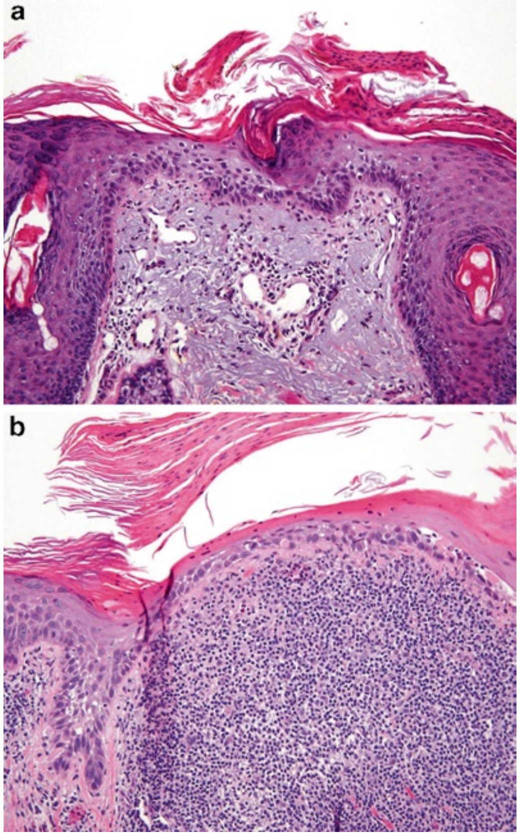

Fig. 2.2 (**a**) Histopathologic section of actinic keratosis stained with hematoxylin and eosin at 20× magnification. Lesion is characterized by alternating ortho- and hyperkeratosis with nuclear atypia and architectural disorder. Keratinocyte atypia approaches full-thickness in middle area of lesion. Note the gray, fragmented nature of the papillary dermis representing extensive solar elastosis. (**b**) Actinic keratosis, lichenoid variant. A brisk lympocytic infiltrate in the papillary dermis accompanies cytologic atypia of epidermal keratinocytes and marked architectural disorder. Numerous apoptotic cells are visible within the epidermis (Courtesy of Wenhua Liu, MD, Consolidated Pathology Consultants, Inc., Libertyville, IL)

Treatment Rationale

Treatment Options for AKs. Given the premalignant potential of AKs, and the metastatic potential of SCC, early treatment is paramount to preventing disease progression. Treatment options for AKs depend on a variety of factors including severity of involvement, duration or persistence of lesions, patient tolerability or desire for cosmesis, affordability/insurance coverage, and physician comfort with available treatment modalities [22, 32].

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