Photodynamic Therapy for Non-Melanoma Skin Cancer

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Key Words

Photodynamic therapy, light-based therapies, cutaneous disorders, skin cancer

Abstract

Photodynamic therapy (PDT) involves the administration of a photosensitizing drug and its subsequent activation by light at wavelengths matching the absorption spectrum of the photosensitizer. Because the skin is readily accessible to light-based therapies, PDT with systemic and particularly with topical agents has become important in treating cutaneous disorders. Topical PDT is indicated for treating actinic keratosis, superficial or thin non-melanoma skin cancer, including some cases of nodular basal cell carcinoma, and some cutaneous lymphomas. Advantages of aminolevulinic acid/methyl aminolevulinate PDT include the possibility of simultaneous treatment of multiple tumors and large surface areas, good cosmesis, and minimal morbidity, such as bleeding, scarring, or infection. (*JNCCN* 2007;5:531–540)

Photodynamic therapy (PDT) is a treatment modality that involves the administration of a photosensitizing drug and its subsequent activation by light at wavelengths matching the absorption spectrum of the photosensitizer.[1,2] After light absorption, energy is transferred to molecular oxygen, yielding reactive singlet oxygen capable of causing direct cellular killing, vascular damage, and local damage by inflammatory and immune mediators.[2] Intracellular singlet oxygen has a diffusion distance of less than 0.1 microns and, because clinical photosensitizers do not accumulate in the cell nucleus, PDT has a very low potential for causing DNA damage.[3]

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Submitted January 23, 2007; accepted for publication February 8, 2007.

This work was supported in part by NCI grants P01CA55791 and P30CA16056.

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Because the skin is readily accessible to light-based therapies, PDT with systemic and particularly with topical agents has become important in treating cutaneous disorders. Current evidence shows topical PDT is effective in treating actinic keratoses (AKs), in situ squamous cell carcinomas (SCCs; Bowen's disease), basal cell carcinomas (BCCs), and cutaneous lymphomas, especially large or numerous lesions or cases in which rapid healing, preservation of function, and superior cosmesis are important. In addition, topical PDT may be used to decrease the size of a large tumor, which can subsequently be removed with a smaller excision.

Photosensitizers

Photosensitizers can be preformed as macrocyclic molecules with red or near-infrared absorptions, such as porfimer sodium (Photofrin), which is approved by the U.S. Food and Drug Administration (FDA) for treating Barrett's esophagus, esophageal cancer, and early- and late-stage lung cancer, or benzoporphyrin derivative (Vertiporfrin), approved for age-related macular degeneration. Photofrin is successfully used off-label for Bowen's disease[4] and BCC[5] at half the dose (1 mg/kg) used for internal sites, although its cost and prolonged cutaneous photosensitivity makes it most indicated for thick or aggressive carcinomas that may not be suitable for topical agents.

In 1990, Kennedy et al.[6] introduced the first practical approach to topical PDT with the photosensitizer precursor 5-aminolevulinic acid (ALA). ALA is a small hydrophilic molecule formed by the enzyme ALA synthetase in an early step in the heme synthetic pathway. The endogenous, fluorescent photosensitizer protoporphyrin IX (PpIX) is the penultimate step in this pathway; the insertion of iron into PpIX forms the nonphotoactive, nonfluorescent heme. All cells synthesize heme, and the pathway is controlled by regulation of

ALA synthetase activity. Exogenous ALA bypasses controls, and if the subsequent rate of formation of PpIX is faster than the rate of conversion of PpIX into heme, a transient accumulation of PpIX occurs. The favorable rate difference and PpIX accumulation occurs in cells of epidermal origin and activated immune and inflammatory cells, but not in mesenchymal cells, including fibroblasts and muscle.[7] Epithelial carcinoma cells preferentially accumulate PpIX because of slower heme conversion with more rapid PpIX synthesis and because defective permeability barriers cause high penetration of ALA. Subsequent irradiation of the lesion with visible light leads to selective destruction of tumor tissue.[6] ALA is available in an alcohol–water–surfactant vehicle as Levulan Kerastick (DUSA, Inc.), which is FDA-approved for AK and also as an extemporaneous preparation in a cream base. Adding a methyl ester to ALA makes the molecule more lipophilic, which may enhance penetration. Once inside the cell, methyl 5-aminolaevulinate (MAL) is converted to ALA by intracellular esterases, a process that can limit the availability of ALA and the accumulation of PpIX. MAL is commercially available as Metvix cream (Galderma), containing 160 mg/g MAL, and MAL-PDT is approved in the United States for treating AK, and in Europe for treating AK, Bowen's disease, and BCC. Metvix cream is not yet available in the United States, but may be marketed along with a light source in 2008.

Topical ALA/MAL-PDT is the most common form of PDT for non-melanoma skin cancer, and is the focus of this article. It is well tolerated and side effects are often mild and transient. Local sensations of burning, pruritus, and stinging are commonly observed during light exposure and may last a few hours after illumination. The pain is probably caused at least partly by PDT effects on cutaneous nerve endings. The pain depends on the amount of PpIX, the light dose rate, and the total absorbed light dose. Fans, skin cooling, local anesthetics (without epinephrine), or conscious sedation may be necessary, depending on the intensity of treatment and surface areas involved. Topical anesthetics may be useful, but should be used with caution when applied with ALA because of ALA's instability at the high pH of many topical anesthetics. Other reported side-effects include local erythema and edema, postinflammatory pigmentary changes, and a brief period of cutaneous photosensitivity.

Light Sources

Both lasers and incoherent light sources, such as lamps and light-emitting diodes, which match the absorption spectrum of the photosensitizer, can be used. PpIX has a complex absorption spectrum with a strong peak at approximately 410 nm (Soret band) and several weaker, longer wavelength Q-bands, the last having a peak at 635 nm.[8] Blue light sources centered around the Soret band efficiently excite PpIX. However, penetration of light into skin depends on wavelength. Below approximately 600 nm, hemoglobin and melanin absorption limit the amount of light that reaches below the dermal vasculature. Thus, blue light is most suitable for thin lesions lying above the dermal capillaries. For thicker lesions that involve the dermis, red light exciting the smaller 635-nm absorption peak is generally preferable. Also, because scattering decreases with wavelength, red light may be effective in treating hyperkeratotic lesions.

Once the wavelengths have been selected, the light exposure dose or fluence (J/cm^2) and the light intensity or irradiance (mW/cm^2) must be chosen. Absorbed, rather than delivered, light is the critical parameter, so the photosensitizer absorption, at the delivered wavelength is important. If adequate oxygenation is present, the PDT dose is dependent on the product of the absorbed light dose and the concentration of PpIX. In terms of PpIX absorption, 10 J/cm^2 at 410 nm is equivalent to more than 150 J/cm^2 at 635 nm. PpIX is auto-oxidized (photobleached) by the singlet oxygen it produces, and is thus consumed during the treatment. Photobleaching provides an upper limit to the amount of photodamage that can be produced, irrespective of the light dose. However, particularly for BCC, to maximize the response rate, the fluence should be sufficient to fully activate the sensitizer. Because of light loss in the skin, thicker lesions require greater light doses. Wide variations in fluences have been used, and few trials have examined the effects of light dose. Work by Oseroff et al.[9] suggests the need for a light dose of at least 100 J/cm^2 at 635 nm. The fluence rate must also be controlled. The photodynamic process consumes molecular oxygen, and too high an irradiance may lead to depletion of intralesion oxygen, making high fluence rates less efficient.[10,11]

AKs

AKs are common premalignant lesions on a continuum that ends in invasive SCC. AK incidence is not

well reported, so the risk for transformation to SCC is difficult to accurately determine; however, it has been estimated to be 5% to 20%.[12] Therefore, AKs are commonly treated.

Based on results of phase II and II studies, the FDA approved ALA-PDT for treating nonhyperkeratotic AK of the face and scalp using the Levulan Kerastick (DUSA Pharmaceuticals Inc.), applied for 14 to 18 hours followed by illumination with a blue light source (Blu-U, 417 nm, 10 J/cm^2, 10 mW/cm^2) for 1000 seconds. In the phase II clinical trial consisting of 36 patients, 85% of AK achieved complete clearance after 1 to 2 treatment sessions.[13] In a phase III trial of 243 patients with nonhyperkeratotic AK, more than 90% of the lesions completely cleared after 1 to 2 treatment sessions.[14] A recent phase IV trial showed a 78% complete clearance rate at 12 months, with a 19% histologically confirmed recurrence rate over 12 months.[15] The overnight ALA application time causes high accumulation of PpIX, and the blue light is efficiently absorbed, giving a high PDT dose that causes substantial discomfort when large surface areas are treated. To condense the treatment into a single session, decrease the discomfort, and permit therapy on entire faces or scalps, investigators have shortened the ALA application time, typically to 1 to 4 hours, or used lower absorbed-light doses. The 585- or 590-nm long-pulsed dye laser,[16,17] the intense pulsed light,[18,19] and various red light sources are commonly used and are effective.[16,20–22] Pain decreases with PDT dose and conditions giving both acceptable response rates with minimal discomfort seem possible to find for most patients, although 2 or more treatment sessions may be necessary.[13,14,19,22–26] With whole-face treatments, ALA-PDT has the added benefit of improving photodamage.[18,19,23]

ALA-PDT is more effective when treating AK on the head compared with the extremities,[17,22] possibly because the skin is more permeable and the AKs tend to be thinner and less hyperkeratotic. The authors have found that ALA-PDT of AK on the extremities is more effective with removal of hyperkeratosis, long ALA application times under occlusion, and high absorbed-light doses. Dragieva et al.[27] showed the importance of the immune system in the response to PDT in a study comparing ALA-PDT for AK and Bowen's disease in immunosuppressed transplant patients and immunocompetent controls. The groups showed comparable complete responses 1 month after treatment, but the immunosuppressed patients experienced much higher recurrence rates. MAL-PDT was also effective for treating AK in transplant recipients in a randomized, placebo-controlled trial.[28] Given the high incidence of AK and Bowen's disease in transplant patients, topical PDT is an important therapeutic option.

In an interesting preliminary study of very low–dose PDT, with the added benefit of ambulation, Zelickson et al.[29] used a chemoluminescent patch (5 cm in diameter) as a light source. The patch emits a broad band of blue light and delivers a total light dose of only 1.7 J/cm^2. The percent clearances for all subjects ranged from 36% to 100%.

Two studies have shown ALA-PDT to be comparable to 5-fluorourasil (5-FU)[21,23] and several studies have compared MAL-PDT with red light to cryotherapy for treating AK (Table 1). After one treatment session, Szeimies et al.[30] showed a slightly better response rate in the cryotherapy group (75% vs. 69% PDT); however, Morton et al.[31] found a significantly higher lesion reduction with PDT (86.9 % vs. 76.2% cryotherapy). Freeman et al.[32] administered 2 treatment sessions and found a statistically significant better response rate in the PDT group (91% vs. 68%). In all 3 studies, however, cosmetic outcome and patient satisfaction were significantly better in PDT-treated patients.[30–32] A randomized trial conducted in the United States of MAL-PDT versus placebo showed an 89% response rate 3 months after 2 treatments, 1 week apart.[33] Although repeated treatment sessions with MAL-PDT are recommended for thick AK, a single treatment session is effective for thin AK.[34]

In conclusion, ALA/MAL-PDT is effective in clearing nonhyperkeratotic AK on the face and scalp, with response rates comparable to topical 5-FU and cryotherapy and better cosmetic outcome than cryotherapy. With ALA-PDT, entire anatomic units, such as the face, can be treated and the delivered PDT dose controlled by choosing the ALA application time, light wavelength, and light dose. Although ALA-PDT is less efficacious when treating hyperkeratotic AK, ALA-PDT with red light is valuable, particularly on the lower legs where destructive modalities have high morbidities.

Bowen's Disease

The intraepidermal neoplasm SCC in situ, or Bowen's disease, is effectively treated with topical PDT.

Table 1 5-Aminolevulinic Acid/Methyl 5-Aminolaevulinate Photodynamic Therapy for Actinic Keratosis*

Investigator	*N* Patients, *N* Lesions	Drug	Application Time (h)	Light Source	Power	*N* Tx	Follow-up (mo)	Response Rate
Jeffes et al.[13]	36 patients, 140 lesions	20% ALA	14–18	Blue light, 417 nm	2–10 J/cm^2	1–2	2	1 Tx 66% 2 Tx 85%
Jeffes[14]	243 patients, 1500 lesions	20% ALA	14–18	Blue light, 417 nm	2–10 J/cm^2	1–2	2	+90%
Calzavara-Pinton[24]	50 lesions	20% ALA	6–8	Dye laser, 630 nm	60–80 J/cm^2, 100 mW/cm^2	+1	24–36	C+H 84%
Fink-Puches et al.[25]	28 patients, 251 lesions	20% ALA	4	UVA or visible light (full spectrum, > 515, > 530, > 570, or > 610 nm)	35–50 J/cm^2	1–2	36	1 Tx 64% 2 Tx 85%
Kurwa et al.[21]	14 patients	20% ALA	4	Red light, 580–740 nm	150 J/cm^2, 86 mW/cm^2	1	6	73
Itoh et al.[22]	10 patients, 53 lesions			Red light, 630–670 nm or red laser, 630 nm		3–6	24	Head 81.8% Ext 55.6%
Varma et al.[20]	127 lesions	20% ALA	4	Red light, 640 nm	100 J/cm^2, 105–168 mW/cm^2	1–2	12	1 Tx 77% 2 Tx 99%
Alexiades-Armenakas and Geronemus[17]	41 patients, 2620 (head) 949 (ext) 53 (trunk)	20% ALA	3 or 14–18	LPDL, 595 nm	4–17.5 J/cm2	1	4	Head 93% Ext 71% Trunk 65%
Piacquadio et al.[26]	243 patients, 4–7 lesions per patient	20% ALA	14–18	Blue light, 417 nm	10 mW/cm^2	1–2	3	91%
Avram and Goldman[18]	17 patients, at least 3 lesions per patient	20% ALA	1	IPL, 560 nm	28–32 J/cm^2	1	3	68%
Zelickson et al.[29]	10 patients, 88 lesions	20% ALA	1	Blue light patch, 431–515 nm	1.7 J/cm^2	1	3	36–100%
Gold et al.[19]	13 patients	20% ALA	0.5–1	IPL, 550–570 nm	34 J/cm^2	3	3	78%
Tschen et al.[15]	110 patients, 968 lesions	20% ALA	14–18	Blue light, 417 nm	10 J/cm^2, 10 mW/cm^2	1–2	12	78%
Szeimies et al.[30]	193 patients, 699 lesions	MAL	3	Red light, 570–670 nm	75 J/cm2	1	3	69%
Pariser et al.[33]	80 patients	MAL	3	Red light, 570–670 nm	75 J/cm^2, 100–200 mW/cm^2	2	3	89%
Freeman et al.[32]	204 patients	MAL	3	Red light, 570–670 nm	75 J/cm^2	2	3	91%
Tarstedt et al.[34]	211 patients, 413 lesions	MAL	3	Red light, 634 nm	37 J/cm^2	1–2	3	1 Tx thin 93% 2 Tx thin 89% 1 Tx thick 70% 2 Tx thick 88%
Morton et al.[31]	119 patients, 758 lesions	MAL	3	Red light, 630 nm	37 J/cm^2	1–2	6	85.8%

*Follow-up greater than 1 month.
Abbreviations: ALA, 5-aminolevulinic acid; C, clinical; Ext, extremities; H, histologic; IPL, intense pulsed light; LPDL, long-pulsed dye laser; MAL, methyl 5-aminolaevulinate; Tx, treatment; UVA, ultraviolet A.

However, with current techniques, ALA/MAL-PDT is not indicated for invasive SCC because of low initial responses and high recurrence rates.[24,35] When treating Bowen's disease, ALA-PDT in combination with red light results in complete response rates ranging from 88% to 100% and low recurrence rates.[20,36–39] Similar to other non-melanoma skin cancers, repeat PDT treatment sessions increase response rates.[20,36–39]

Morton et al.[38] extensively studied ALA-PDT for the treatment of Bowen's disease. Red light (630 nm) was found to be superior to green light (540 nm) in complete clearance and recurrence rates. ALA-PDT was advocated as the first-line therapy for large or multiple patches of Bowen's disease, achieving clearance rates of 79% and 89%, respectively, at a 1-year follow-up.[36] ALA-PDT was found to be at least as effective as cryosurgery with fewer adverse effects.[37] It also was found to be superior to 5-FU for the treatment of Bowen's disease with complete response rates of 88% and 67%, respectively, and with no 5-FU–associated ulceration or scarring in the PDT group.[39] MAL-PDT also was shown to be superior to 5-FU and cryotherapy for the treatment of Bowen's disease.[40] MAL-PDT has been approved for Bowen's disease in Europe and Australia, and topical ALA-PDT for Bowen's disease was supported in a February 2006 National Institute of Health and Clinical Excellence (NICE) guidance in Britain.

In conclusion, PDT can be considered primary treatment for Bowen's disease in patients with large or multiple lesions and for anatomically difficult treatment areas, including patches involving poor healing sites (Table 2).

BCCs

BCC is a slow-growing malignancy derived from the undifferentiated basal layer of the epidermis. It is the most common type of cutaneous malignancy and the most frequent malignant disease that fair-skinned people acquire in a lifetime.[41] In addition, many patients develop multiple BCCs. Individuals with the nevoid basal cell carcinoma syndrome (NBCCS)/Gorlin-Goltz syndrome who have a mutation in one copy of the patched gene may develop tens to hundreds of BCCs each year starting in childhood.[9] BCCs have multiple phenotypic and histologic subtypes; the most common are superficial (sBCC) and nodular (nBCC). sBCCs are thin lesions budding down from the epidermis, typically with permeable stratum corneum. nBCCs are thicker with islands of carcinoma in the dermis, often with a relatively intact stratum corneum.

Topical ALA-PDT has been studied extensively for the treatment of sBCC and nBCC. Topical PDT is clearly efficacious for sBCC and as effective as cryotherapy, with the additional benefit of superior healing and cosmesis.[42] Patients with large and multiple sBCC may particularly benefit from ALA-PDT,[36] including individuals with NBCCS. These patients have multiple BCCs and typically undergo numerous

Table 2 5-Aminolevulinic Acid/Methyl 5-Aminolaevulinate Photodynamic Therapy for Bowen's Disease

Investigator	*N* Lesions	Drug	Application Time (h)	Light Source	Power	*N* Tx	Follow-up (mo)	Response Rate	Recurrence Rate
Morton et al.[37]	20	ALA	4	Xenon short arc, 630 nm	120–134 J/cm^2, 50–100 mW/cm^2	1–2	12	100%	
Morton et al.[38]	61	ALA	4	Xenon short arc, 540 nm or 630 nm	62.5 or 125 J/cm^2, 86 mW/cm^2	1–2	7–10	540 nm: 72% 630 nm: 94%	540 nm: 33% 630 nm: 7%
Morton et al.[36]	40 (> 20 mm) 44 (< 20 mm)	ALA	4	Xenon short arc, 630 nm	125 J/cm^2, 50–100 mW/cm^2	1–3	12	> 20 mm: 88% < 20 mm: 98%	> 20 mm: 11% < 20 mm: 9%
Varma et al.[20]	50	ALA	4	Red light, 640 nm	105 J/cm^2, 105–168 mW/cm^2	1–2	12	88%	31%
Salim et al.[39]	33	ALA	4	Xenon short arc, 630 nm	100 J/cm^2, 50–90 mW/cm^2	1–2	12	88%	7%
Morton et al.[40]	96	MAL	3	Red light, 570–670 nm	75 J/cm^2	1–2	12	80%	

Abbreviations: ALA, 5-aminolevulinic acid; MAL, methyl 5-aminolaevulinate; Tx, treatment.

surgical procedures, leaving them with disfiguring scars. Children with NBCCS are a significant therapeutic concern because they may have disease extending over large surface areas. ALA-PDT has permitted clearance of BCC without scarring[9] and is arguably the preferred treatment for BCC in children and adolescents. Although not registered in the United States, ALA-PDT for sBCC is supported by the 2006 NICE guidance in Britain.

In developing the therapy, investigators explored a wide range of treatment parameters. ALA application times have varied from 3 to 24 hours, light wavelengths from blue to red, and light doses from less than 20 J/cm^2 to more than 200 J/cm^2. The numbers of initial treatments of the carcinoma also vary. Differences in clinical response rates, ranging from 79% to 100%,[6,20,24,35,36,43] and recurrence rates (Table 3) reflect differences in treatment conditions. Outcome is expected to depend on adequate levels of PpIX and absorbed light in the lesion. Morton et al.[44] found that 6 hours of ALA application gave a better outcome than 4 hours and that a 630 ± 15 nm red light was more effective than a 540 ± 15 nm green light.[38] A statistically significant difference in the cure rate and cosmetic outcome between a red lamp with continuous spectrum (570–740 nm) and a red laser (630 nm) has not been found.[45,46]

Oseroff et al.[9] examined the relationship between light dose and BCC response in 3 children using a 633-nm laser at 150 mW/cm^2 and found a threshold of 100 to 150 J/cm^2 for maximal efficacy. In adult sBCC treated with a 200 J/cm^2 light dose at 150 mW/cm^2 and a 4- to 6-hour ALA application time, these authors found 89% to 96% complete responses with a single treatment of 394 carcinomas (unpublished data). As shown in Table 3, through re-treating the fraction of lesions that are not complete responses, comparable results have been obtained by others[20,36] using 100 to 170 J/cm^2 narrow-band red light and 1 to 2 treatments. Several clinical studies report an increase in initial response rate with a lower recurrence rate after repeated PDT sessions.[20,24,36,42,43,47,48] Because ALA/MAL-PDT is minimally scarring, recurrences are readily apparent and can be re-treated easily. An interesting study by de Haas et al.[46] found that splitting the treatment into 20 J/cm^2 and 80 J/cm^2 fractions separated by 2 hours significantly improved the response rate to 97%.

ALA-PDT is less effective for nBCC.[24,43] ALA-PDT may be less efficacious when treating nBCC because of the limited depth of tissue penetration[49] or the lower permeability of the stratum corneum. Therefore, methods have been used to reduce tumor volume and enhance penetration of ALA, such as an initial debulking procedure and using dimethylsulfoxide (DMSO). Studies that include these methods when treating nBCC have achieved response rates of 92%[50,51] with low recurrence rates at 1 year.[50] However, longer follow-up data are necessary to better assess the value of DMSO.

Another method to increase PpIX accumulation in thick lesions is the application of an iron chelator, such as desferrioxamine (DF) or ethylenediaminetetraacetic acid disodium (EDTA). Because iron is required for the conversion of PpIX to heme, an iron chelator will thus increase PpIX concentration. Fijan et al.[47] used DF in conjunction with ALA-PDT; however, because clinical response rates were similar to those of studies not using DF. DF does not seem to confer additional benefit in ALA-PDT of non-melanoma skin cancers. However, EDTA + DMSO increased clinical lesion clearance rates from 67% to 90% for nBCCs less than 2 mm and from 34% to 50% for thicker lesions.[52] Note that iron chelators might be undesirable because they could potentially reduce differences in iron metabolism between normal and lesional tissue, thus reducing the selectivity of the treatment.[53]

MAL-PDT is also an effective treatment modality for sBCC and nBCC[54] (Table 3). In Europe, where Mohs surgery is less common than in the United States, several studies advocate the use of MAL-PDT for "difficult-to-treat" and "recurrent" BCC.[48,55,56] Typically, MAL-PDT treatment consists of a cycle of 2 PDT treatments 1 week apart, repeated after 3 months on carcinomas that did not fully respond. MAL-PDT was cosmetically superior although not as durable as excisional surgery in treating primary nBCC.[57] It is approved in Europe for both superficial and nodular BCC.

Cutaneous T-Cell and B-Cell Lymphoma

ALA-PDT has been used to treat cutaneous T-cell lymphoma in published case reports. Treatment is based on in vitro studies that showed PpIX accumulation in lymphocytes with both B- and T-cell toxicity after PDT.[7,58]

ALA-PDT is effective when treating plaque and stage I, stage III, classic, CD30, and CD8 cutaneous T-cell lymphoma.[59–65] Although a low light dose was effective for stage I lesions, an increase in total light

Table 3 5-Aminolevulinic Acid/Methyl 5-Aminolaevulinate Photodynamic Therapy for Basal Cell Carcinoma

Investigator	*N* Lesions	Drug, Pre-Tx	Application Time (h)	Light Source	Power	*N* Tx	Follow-up (mo)	Response Rate	Recurrence Rate
Kennedy et al.[6]	300 S	ALA	3–6	Filtered red, 600 nm		1	3	C 79%	
Svanberg et al.[43]	55 S 25 N	ALA	4–6	Nd:YAG laser, 630 nm	60 J/cm^2, 110 mW/cm^2	1–2	6–14	1 Tx CS 100% 1 Tx CN 64% 2 Tx CN 100%	
Calzavara-Pinton[24]	23 S 30 N 4 P	ALA	6–8	Dye laser, 630 nm	60–80 J/cm^2	1–8	24–36	CS+HS 86.9% CN+HN 50% CP+HP 0%	
Fink-Puches et al.[35]	95 S	ALA	4	UVA or visible light (full spectrum, > 515, > 570, or > 610 nm)	UVA, 1.1 J/cm^2, visible light, 18–131 J/cm^2	1	3–60	C 86%	44%
Soler et al.[50]	119 N	ALA Debulk DMSO	3				12–26	C 92%	5%
Soler et al.[45]	245 S	ALA DMSO EDTA	3	Red laser, 630 nm or red light, 570–740 nm	Red laser, 102 J/cm^2 red light 192 J/cm^2	1	6	Red laser: C 86% Red light: C 82%	
Thissen et al.[51]	24 N	ALA Debulk	6	Red light, 630–635 nm	120 J/cm^2, 100 mW/cm^2	1	3	C 92% H 92%	
Morton et al.[36]	40 large		6	Red light, 630 nm	120–134 J/cm^2, 50–100 mW/cm^2	1–3	12–60	C 88%	11%
Varma et al.[20]	62 S	ALA	6	Red light, 640 nm	105 J/cm^2, 105–168 mW/cm^2	1–2	12	C 95%	18%
Wang et al.[42]	22 S 25 N	ALA	6	Nd:YAG laser, 635 nm	60 J/cm^2, 80–20 mW/cm^2	1–5	12		C 5% H 25%
Fijan et al.[47]	34 S 22 N	ALA DF	20	Halogen, red filter	300 J/cm^2, 150–250 mW/cm^2	1–2	6	1 Tx CS 88.2% 2 Tx CS 97% 1 Tx CN 31.8% 2 Tx CN 59.2%	
de Haas et al.[46]	505 S	ALA	4 or 4 + 6	Diode laser or LED or red light, 590–650 nm	75 or 20 + 80 J/cm^2, 50 mW/cm^2	1	12	1 Ill 89% 2 Ill 97%	
Soler et al.[54]	131 S 82 < 2 mm 86 > 2 mm 6 BCC 3 mixed 2 Mo	MAL Debulk	2.5–24	Halogen, 570–670 nm	50–200 J/cm^2	1–4	24–48	C all 89% CS 91% C < 2 mm 93% C > 2 mm 86% BCC 100% Mixed 66% Mo 0%	All 11% S 9 < 2 mm 7% > 2 mm 14% BCC 0% Mixed 33%
Horn et al.[55]	49 S 52 N 7 mixed	MAL Debulk	3	Red light, 570–670 nm	75 J/cm^2	1–4	24	C all 87% CS 92% CN 87% C mixed 57% H all 77% HS 85% HN 75% H mixed 43	S 22% N 14% Mixed 0%

Table 3 Continued									
Vinciullo et al.[56]	74 S 27 N 30 mixed	MAL Debulk	3	Red light, 570–670 nm	75 J/cm^2	1–4	24	H all 89% HS 93% HN 82% H mixed 86%	All 22% S 18% N 33% Mixed 19%
Rhodes et al.[57]	53 N	MAL	3	Red light, 570–670 nm	75 J/cm^2	1–4	24	C 91%	10%

Abbreviations: ALA, 5-aminolevulinic acid; BCC, basal cell carcinoma; C, clinical; DF, desferrioxamine; DMSO, dimethylsulfoxide; EDTA, ethylenediamine tetraacetic acid disodium; H, histologic; Ill, illumination; LED, light-emitting diode; MAL, methyl 5-aminolaevulinate; Mo, morpheaform; N, nodular; P, pigmented; S, superficial; Tx, treatment.

dose was more effective for stage III lesions.[62] Markham et al.[63] reported success after treating a tumor stage lesion, yet Edstrom et al.[64] found tumor lesions to be unresponsive to ALA-PDT. Topical PDT is likely to be most useful for slowing proliferating or stable lesions (Table 4).

PDT is useful for cutaneous T-cell lymphoma in problem locations because it is tissue-sparing, has few side effects, can be repeated as often as necessary, and achieves good cosmetic results. It does not preclude subsequent use of electron beam or spot radiation therapy and can be safely used after full-dose radiation.

Mori et al.[66] recently reported the effectiveness of PDT in treating 3 patients with cutaneous B-cell lymphoma; 1 received MAL and 2 received ALA. The light source was a light-emitting diode lamp (630 nm, 37 J/cm^2, 70–100 MW/cm^2). Patients underwent 1 to 2 treatment sessions and a complete response was noted at follow-up of 8 to 24 months.[66]

Conclusions

Topical PDT is indicated for treating AK, superficial or thin non-melanoma skin cancer, including some

Table 4 5-Aminolevulinic Acid Photodynamic Therapy for Cutaneous T-Cell Lymphoma

Investigator	*N* Lesions *N* Patients,	Application Time (h)	Light Source	Power	*N* Tx	Follow-Up (mo)	Response Rate
Svanberg et al.[43]	2 patients 4 lesions	4–6	Nd:YAG laser, 630 nm	60 J/cm^2, 110 mW/cm^2	1–2	6–14	50%
Wolf et al.[61]	2 patients Plaque MF	4–6	Leica P-2000 slide projector	40 J/cm^2	4–5	3–6	C+H 100%
Orenstein et al.[62]	2 patients Stage I MF: 1 lesion Stage III MF: 5 lesions	16	Red light, 580–720 nm	170–380 J/cm^2	1–2	24–27	Stage I: 100% Stage III: 100%
Markham et al.[63]	1 patient Tumor MF: 1 lesion	4	Red light, 580-740 nm	20 J/cm^2, 20 mW/cm^2	5	24	100%
Edstrom et al.[64]	10 patients Plaque MF: 10 lesions Tumor MF: 2 lesions	5–6	Red light, 600–730 nm	88–180 J/cm^2, 20–265 mW/cm^2	2–11		Plaque MF: 78% Tumor MF: 0%
Paech et al.[59]	1 HIV patient Plaque MF	4	Red light	180 J/cm^2	2		100%
Leman et al.[60]	1 patient Plaque MF: 2 lesions	6–24	Red light	100 J/cm^2	4		C+H 100%
Coors et al.[65]	4 patients Classic MF: 4 lesions CD30+ CTCL: 2 lesions CD8+ CTCL: 1 lesion	6	Red light	96–144 J/cm^2	1–7	14–18	100%

Abbreviations: C, clinical; CTCL, cutaneous T-cell lymphoma; H, histologic; MF, mycosis fungoides; Tx, treatment.

cases of nBCC, and some cutaneous lymphomas. Advantages of ALA/MAL-PDT include the possibility of simultaneous treatment of multiple tumors and large surface areas, good cosmesis, and minimal morbidity, such as bleeding, scarring, or infection. PDT is a noninvasive approach and large areas can be treated repeatedly. It is useful in patients who refuse surgery or are not good surgical candidates. In some circumstances, PDT can be an effective adjuvant to reduce lesion size before Mohs surgery, especially when surgery may lead to a large defect or little healthy skin is present for reconstruction.[56]

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