Seminars in Cutaneous Medicine and Surgery

Topical Treatment Strategies for Non-Melanoma Skin Cancer and Precursor Lesions

S. Teri McGillis, MD, and Howard Fein, MD

The ability to manage non-melanoma skin cancers and pre-malignant lesions with topical pharmacologic agents is highly compelling. This article examines currently available products and discusses their emerging roles and limitations. These include fluorouracil, diclofenac sodium, imiquimod, and photodynamic therapy.
Semin Cutan Med Surg 23:174-183

Dermatologists practice in the midst of a skin cancer epidemic. The incidence of both basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) continues to rise. In 2005, approximately 1.5 million of these non-melanoma skin cancers (NMSC) will be treated in the United States. It is therefore essential for those trained in cutaneous oncology to not only diagnose these tumors but to offer effective and appropriate treatment. A significant proportion of NMSC is already invasive at the time of initial clinical presentation and will require definitive surgical intervention. However, aggressive nonsurgical treatment of precancerous lesions and early superficial lesions may decrease the rate of conversion to more advanced tumors. The use of topical pharmacologic intervention to retard tumor progression is clearly a topic of immense interest.

The concept of nonsurgical NMSC treatment is appealing to both prospective patients and physicians alike. As such, several pharmacologic alternatives are already available for the treatment of actinic keratoses (AK), with many more being rapidly developed and tested. Several are also being evaluated for their effectiveness in treating superficial forms of NMSC. In an effort to delineate the proper use and indications for these nonsurgical modalities, this article will examine the prevailing topical AK and NMSC therapies which at the time of publication include fluorouracil, diclofenac sodium, imiquimod, and topical photodynamic therapy (PDT) with 5-aminolevulinic acid (ALA).

Department of Dermatology, Section of Dermatologic Surgery, Cleveland Clinic Foundation, Cleveland, OH

Address reprints to S. Teri McGillis, MD, Department of Dermatology, Cleveland Clinic Foundation, 9500 Euclid Avenue, Bldg. A-61, Cleveland, OH 44195. E-mail: mcgillt@ccf.org

Pathology/Epidemiology

Pre-cancerous lesions known as AK are evolving cutaneous neoplasms comprising atypical keratinocytes. It has been proposed that AK be more accurately classified according to a grading system that would emphasize their progressive evolution toward SCC.[1] Similar systems are adopted by gynecologists for grading cervical intraepithelial neoplasias. AK and SCC share multiple genomic mutations which emphasizes their commonality.[2] Increases in p53 mutations have been identified in sun-exposed skin, AK, and SCC.[3,4] Growth hormone receptor expression may also be a marker of progression from hypertrophic AK into SCC.[5]

Although the precise rate is unclear, it has been generally accepted that anywhere from 0.25 to 1% of AK convert to SCC each year. In a recent review, it was found that 82% of SCC arose from or were in close proximity to AK.[6] Studies suggest that the presence of AK is more strongly associated with developing SCC than any other factor such as age, gender, or skin type.[7,8] With over 4 million patient visits for AK each year, these lesions present a significant opportunity to impact the NMSC epidemic.

Clinically, AK are characterized as scaly, crusted, keratotic papules and plaques occurring on sun-exposed areas such as the face and upper extremities. They are often associated with epidermal atrophy and other signs of photodamage. Many variants of AK exist including a proliferative type that exhibits more aggressive behavior.[9] Without histologic evaluation, AK can be difficult to distinguish clinically from frank SCC. Certainly, the correct diagnosis is critical to effective treatment.

BCC, the most common type of NMSC, also typically occurs on areas chronically exposed to ultraviolet radiation (UVR). Unlike SCC, a precursor lesion has yet to be defined for BCC. BCC is thought to arise from pleuripotential stem cells located in the basal layer of the epidermis. Although

 1085-5629/04/$-see front matter
doi:10.1016/j.sder.2004.06.005

several invasive forms of BCC exist, only the superficial types should be considered candidates for nonsurgical intervention.

Topical Therapies for AK and NMSC

Destructive modalities such as cryosurgery and electrodessication and curettage represent approximately 80% of all initial treatments rendered in the United States for AK.[10] While highly effective, these procedures often require local anesthesia and can result in scarring and pigmentary alterations. These procedures are ideally performed on isolated or limited numbers of lesions (<10).

Widespread and numerous lesions are best approached in a "field-effect" wherein all suspected areas of keratinocyte dysplasia are treated within a given region; this strategy is often useful in identifying and treating areas of subclinical disease. Previous methods aimed at eradicating large areas of AK have been primarily surgical and have included such procedures as dermabrasion, ablative laser resurfacing, and chemical peeling. Although these surgical treatments are effective, their ultimate usefulness has been limited by prolonged postoperative recovery time, direct patient cost, and potential side-effect profile. Consequentially, this has led to the development of a variety of pharmacologic alternatives, many of which compete with more familiar therapeutics such as fluorouracil. Newer formulations of fluorouracil and newer products such as diclofenac sodium can be added to the AK treatment armamentarium. Imiquimod and PDT show promise for treating not only AK but NMSC as well.

Fluorouracil

Topical formulations are available as Efudex 5%, 2% (Valeant Pharmaceuticals, Int., Costa Mesa, CA), Fluoroplex 1% (Allergan, Inc., Irvine, CA), and Carac 0.5% (Dermik Laboratories, Berwyn, PA). Fluorouracil (5-FU) is an antineoplastic pyrimidine analog. It functions as an antimetabolite where it interferes with DNA, and to a lesser extent, RNA synthesis by blocking the methylation of deoxyuridylic acid into thymidylic acid. Atypical keratinocytes are preferentially targeted in part because of their higher cellular reproduction rates but also by virtue of having a more permeable cell-membrane barrier.

The 5% 5-FU formulation was approved as a treatment of AK in the early 1970s, despite the fact that formal FDA phase III trials were never completed. The 5% formulation which is typically applied twice daily for a 2- to 4-week duration has remained the gold standard to which other topical AK treatments are compared (Table 1). To date, no generic alternatives exist. The overall effectiveness in the treatment of AK (partial and complete clearance) is 92 and 82%, respectively. In practice, the cure rate with topical 5-FU is to some extent reflected by the degree of erythema, erosions, and eventual crusting which develops at treatment sites. Anecdotally, patients with an intense inflammatory response often attain the best clinical response, a finding which often frustrates patients and physician alike.

In an effort to make topical 5-FU therapy more palatable to

Table 1 Comparison of FDA-Approved Topical AK Treatments

Product	Formulation	Approval	Drug Activity	Dosing Duration	Approved Sites	Cutaneous Reaction	Pregnancy Category	Cost	Comments
Efudex	5%, 2% Fluorouracil	1970	Antimetabolite	BID for 2-4 weeks	Any	4+	X	$	Gold Standard, highest potency fluorouracil, also approved for superficial BCC
Fluoroplex	1% Fluorouracil	1970	Antimetabolite	BID for 2-6 weeks	Any	3+	X	$	Longer treatment periods may be needed, data not available
Carac	0.5% Fluorouracil and 0.35% microsponge	2001	Antimetabolite	QD for 2-4 weeks	Face and scalp	2-4+	X	$	Once daily use may improve compliance
Solaraze	3% Diclofenac sodium and hyaluronic acid	2002	COX-2 inhibitor	BID for 8-12 weeks	Any	2+	B	$$	Lower efficacy rates, may cause contact dermatitis, safest in pregnancy
Aldara	5% Imiquimod	2004	Immune response modifier	BIW for 16 weeks	Face and scalp	2-4+	C	$$$	Novel drug class, prolonged treatment regimens may increase cost

patients, physicians have resorted to a variety of "off-label" treatment protocols. Pulsed regimens, differing dosing routines, and combination approaches such as use in conjunction with chemical peeling agents have all been used with variable success.[11-13]

For most patients, however, the authors prefer to initiate therapy with twice daily application of 5% 5-FU cream. The usual treatment duration is 2 to 4 weeks for AK and up to 4 to 6 weeks for superficial BCC. Patients or areas that are "nonreactive" may respond to combination therapy with 0.5% tretinoin cream, which is applied once daily in addition to the 5-FU cream. Immunocompromised patients and other patients with extensive amounts of photodamage are approached one body surface region at a time (ie, the face or arms) to limit potential treatment discomfort. Thicker, hypertrophic lesions should be treated first with cryosurgery, gentle curettage, or even "primed" with applications of tretinoin cream, lactic acid moisturizers, or short courses of topical diclofenac sodium before the initiation of 5-FU cream. A biopsy should be obtained from any nonresponding or persistent lesions to exclude the possibility of SCC. An absolute reduction in the number of AK or in the need for further intervention should be considered a 5-FU treatment success.

Recently, a novel fluorouracil cream that contains 0.5% fluorouracil in a microsphere vehicle was approved for AK therapy. This lower dose formulation decreases, but does not eliminate, potential cutaneous irritation. In the authors' experience, however, more rigorous reactions or longer treatment times are often necessary to achieve maximal therapeutic effects. Interestingly, this formula has only been FDA approved for the treatment of AK located on the face and anterior scalp. Efficacy data show 75% of all patients (rather than lesions) experienced partial clearance and 55% of patients had total clearance. In one side-to-side study, 0.5% fluorouracil cream compared favorably to the 5.0% formulation in the reduction and clearance of AK. All patients experienced cutaneous irritation; however, the once daily application of 0.5% was preferred.[14] Unlike higher strength formulations, the authors are unaware of any data which support the use of 0.5% fluorouracil for the treatment of NMSC.

The authors regard only the 5% fluorouracil formulation as an appropriate treatment for superficial BCC and, in selected cases, SCC in situ, where its effectiveness has also been documented.[15,16] In FDA studies, the complete clearance rate (CR) for superficial BCC following 5% fluorouracil therapy approached 93%. A small pilot study with short follow-up showed that combining 5-FU with phosphytidal choline as a transepidermal carrier could achieve a CR of 90% for moderate thickness BCC as well, compared with 57% using 5-FU in petrolatum.[17] As in any nonsurgical NMSC treatment, response to therapy must be carefully monitored. Persistent or nonresponding lesions require biopsy and, depending on the pathology, definitive surgical treatment. In patients with extensive areas of photodamage, superficial BCC may be admixed within a field of AK and at times appear clinically indistinguishable. In these instances, 5% fluorouracil may be applied in a "field effect" to an entire body segment to effectively treat both conditions.

In addition to treating AK and BCC, 5-FU is useful for delineating tumor margins before a definitive surgical procedure. Superficial tumors such as SCC in situ, extra mammary Paget's disease, and BCC will preferentially become inflamed following twice daily preoperative applications of 5% fluorouracil cream. Preoperative treatment periods of 7 to 10 days are typically sufficient for this" chemical highlighting" to occur (Fig. 1). Similarly, imiquimod cream applied three times weekly for 3 to 4 weeks will accomplish similar results.

Dehydropyrimidine Dehydrogenase Deficiency (DPD)

Dehydropyrimidine dehydrogenase is the primary enzyme involved in degradation of 5-FU. Its absence results in shunting of 5-FU to an anabolic pathway. Approximately 3% of the population is estimated to be DPD deficient for the heterozygous state. DPD-deficient patients who receive systemic 5-FU for the treatment of internal malignancies may develop toxic side effects which include stomatitis, diarrhea, neutropenia, thrombocytopenia, and neurotoxicity. However, the adverse effects associated with the use of topical 5-FU products are extremely rare (1 in 1,000,000). Nevertheless, therapy with topical 5-FU cream is contraindicated in patients with known DPD deficiency.

Diclofenac Sodium Gel (3%)

Diclofenac sodium (Solaraze, Bioglan Pharmaceuticals Co., Malvern, PA) gel is a topical nonsteroidal anti-inflammatory drug (NSAID) FDA-approved for the treatment of AK. Its mechanism of action remains elusive but likely relates to its nonspecific inhibition of the cyclooxygenase (COX) isoenzymes, COX-1 and COX-2. COX-1 is constitutively expressed in almost all tissues, while COX-2 is an inducible enzyme expressed at sites of inflammation or neoplasia. Both AK and SCC express COX-2 protein more strongly than normal keratinocytes.[18]

The authors regard diclofenac sodium as an alternative therapy for patients who are not willing to endure the side effects associated with traditional 5-FU treatment. Cutaneous reactions, however, are not eliminated entirely and allergic contact dermatitis has been reported in association with topical diclofenac sodium. Previously masoprocol (Actinex), another NSAID, was approved for topical use in the early 1980s but was subsequently withdrawn from the U.S. market in 1996 over similar concerns of contact sensitization.

The typical dosing regimen for diclofenac sodium involves twice daily application for periods lasting up to 3 months. Patient compliance is remarkably good despite the prolonged treatment interval. Anecdotally, some patients have reported marked improvements in skin texture following its use. The overall efficacy in treating AK appears to be less than that reported with 5-FU formulations. CR was achieved in just 47% of patients, 30 days following treatment for facial lesions as compared with 19% of pa-

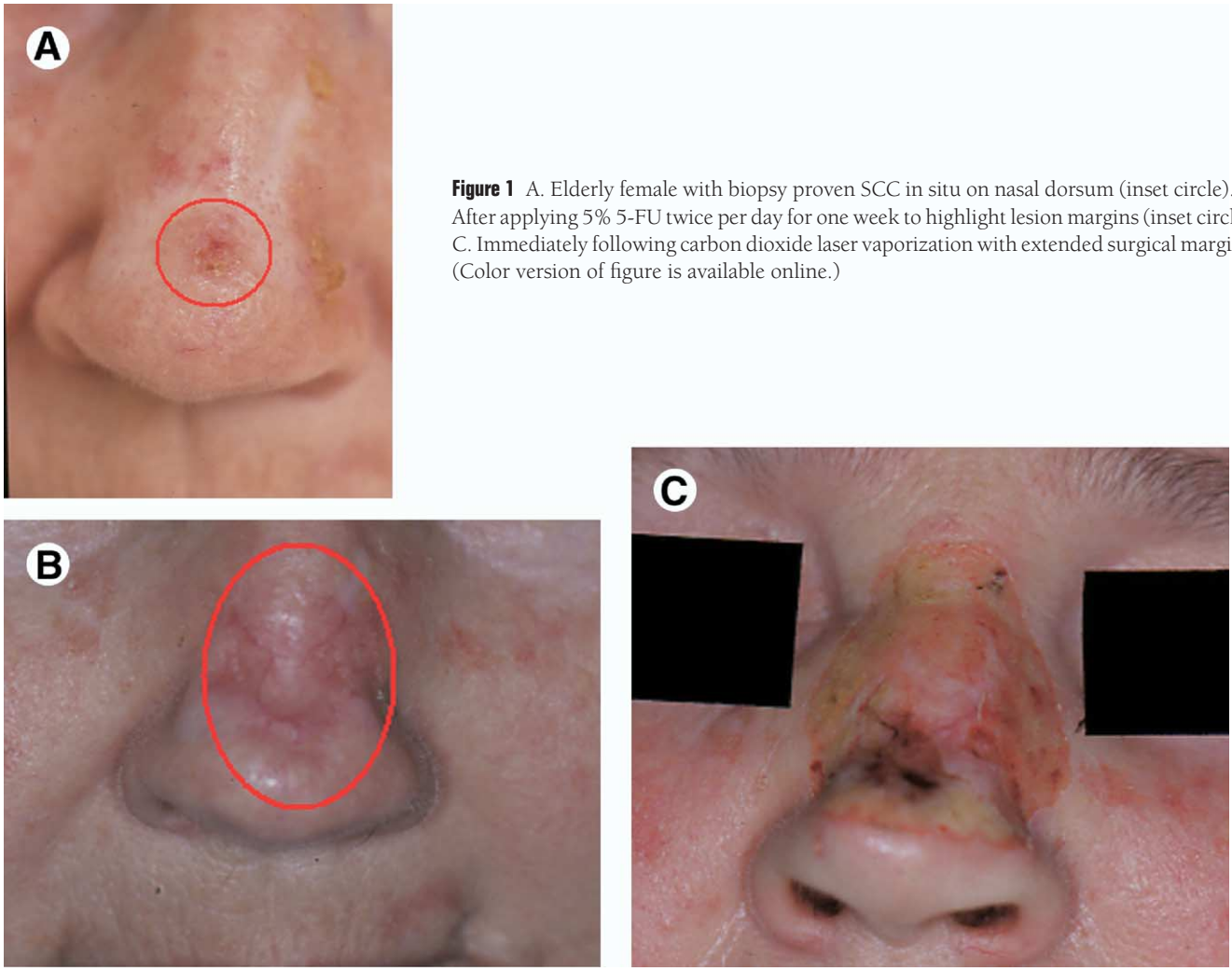

Figure 1 A. Elderly female with biopsy proven SCC in situ on nasal dorsum (inset circle). B. After applying 5% 5-FU twice per day for one week to highlight lesion margins (inset circle). C. Immediately following carbon dioxide laser vaporization with extended surgical margins. (Color version of figure is available online.)

tients in a placebo group (Solaraze literature). Efficacy for treating AK located on other body sites was lower.

Although topical diclofenac sodium is generally a well-tolerated medication, its use should be avoided in patients with known bleeding diatheses, ASA triad syndrome, or documented NSAID hypersensitivity. Perhaps the true hidden value of diclofenac sodium may be in its pregnancy category B classification, which compares favorably to the X designation given to topical 5-FU. With many patients leading increasingly active outdoor lifestyles and with the popularity of tanning beds, it is no longer unusual to treat AK and NMSC in women of childbearing age.

Multi-center phase II and III tumor chemoprevention studies are now being conducted using systemic celecoxib (Celebrex), which is a highly selective COX-2 inhibitor. At the present time, however, there is no evidence to support the use of topical diclofenac sodium in either the treatment or the prevention of BCC or SCC.

Table 2 Topical Imiquimod 5% in the Treatment of Basal Cell Carcinoma

Reference	Dosing Regiment	Number of Patients Treated	Clearance Rate
Shumack et al[26]	QD for 6 weeks	35	71%
	QD for 12 weeeks	21	76%
Huber et al[27]	TIW for 12 weeks	15	100% at 18 months follow-up
Geisse et al[63]	BID for 12 weeks	10	100%
	QD for 12 weeks	31	87%
	QD, 5 Days/week for 12 weeks	26	81%
	TIW for 12 weeks	29	52%

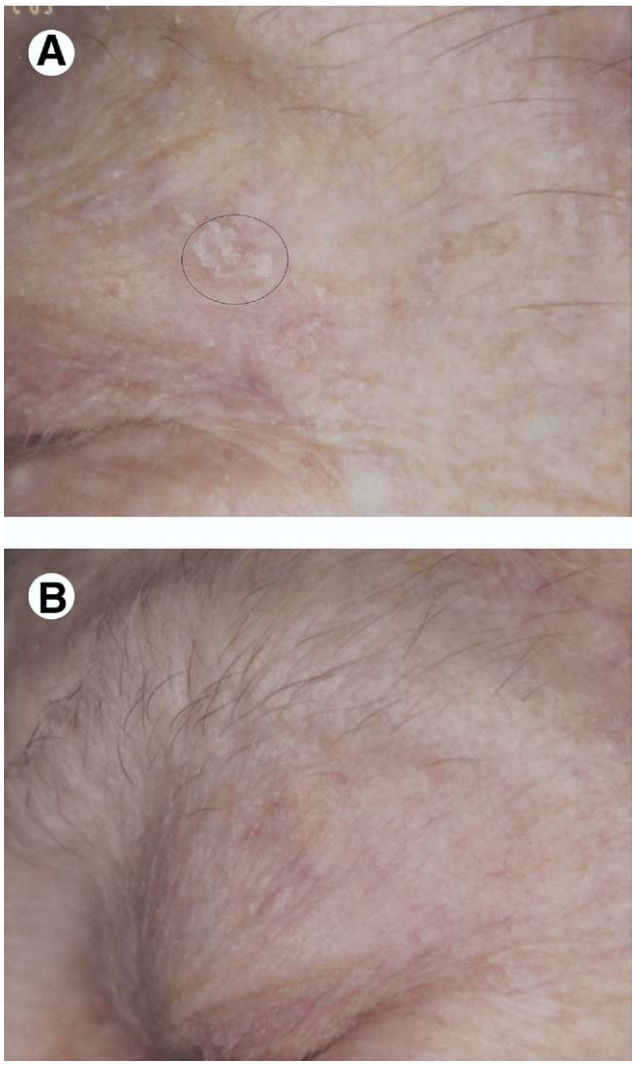

Figure 2 Top: Biopsy proven SCC in situ on upper eyelid before treatment. Bottom: After 7 weeks of topical TIW imiquimod treatment. (Color version of figure is available online.)

Imiquimod

In March of 2004, 5% imiquimod (Aldara, 3M Pharmaceuticals, St. Paul, MN), an immune response modifier, became the latest treatment for AK approved by the FDA. Previously, imiquimod had been widely used as a treatment for genital and common warts. The mechanism of action in treating AK is not known. The drug has many cellular effects that result in stimulating TH-1 innate immunity. Imiquimod's effects are mediated after binding to a unique receptor known as Toll-like receptor 7 (TLR-7) that is found on dendritic cells and monocytes. TLR-7 activation up-regulates a myriad of cytokines including interferons, tumor necrosis factor, and interleukins. TLR-7 also is involved in the regulation of cellular apoptosis. Following imiquimod treatment, immunologic memory is said to be established, a finding which may contribute to ongoing surveillance and continued response post-treatment. This aspect alone, if proven, would distinguish this drug from others in its treatment class. It is known from experience in the treatment of verrucae and condyloma that a significant percentage of patients will fail to attain an adequate clinical response with topical imiquimod therapy. In fact, molecular differences for clinical responders and nonresponders have even been identified.[19] Whether or not there are true nonresponders to AK therapy has not yet been established.

According to its FDA approval for the treatment of AK, imiquimod is to be used bi-weekly, unoccluded, for 16 weeks. This extended treatment period rivals that of diclofenac sodium. However, our own personal experience suggests that the actual frequency and duration of treatment varies greatly and that the dosing regimen should be titrated to produce an irritant "cytokine" dermatitis, which appears necessary for achieving optimal effect. This immune reaction clinically resembles the cutaneous reactions induced by fluorouracil, yet is remarkably devoid of discomfort.

Success using cyclic applications has also been previously described.[20] The product is applied three times a week for 4 weeks (a single 12 sachet box is prescribed), carefully monitoring the skin for response. A rest period can then occur for up to 4 weeks at which time the product is applied for an additional 4 to 6 weeks if needed. The treatment surface area is limited only by the sachet size, which covers up to 25 cm^2.

Efficacy data from FDA trials demonstrated that 46% of patients completely cleared all baseline AK as well as any subclinical lesions that appeared during treatment. Only 3% of patients using the vehicle cream cleared. Patients who cleared 75% or more of their baseline lesions were defined as partially clear and 60% of patients achieved this state compared with 10% of vehicle users.

Over the past few years, multiple case reports have been published which support the use of imiquimod cream as a potential treatment for both BCC and SCC in situ.[21-25] In a company-sponsored, FDA phase II trial for the treatment of nodular BCC daily, once daily dosing with imiquimod resulted in a clearance rate of 71% of patients at 6 weeks and 76% at 12 weeks.[26] In a subsequent open-label series which also examined the efficacy of imiquimod in the treatment of nodular BCC, a CR was reported in 100% of patients with zero recurrences over an 18-month follow-up period.[27] In a similar phase II Australian study involving patients with SCC in situ, complete clearance was reported in 15/16 lesions following once daily application of imiquimod for 16 weeks duration.[28] While the data from these preliminary reports are nonetheless encouraging, the results from a recently completed, randomized phase III study are currently being evaluated by the FDA and will be used to determine imiquimod's true efficacy in the treatment of BCC (Table 2).

An exact dosing regimen for treating NMSC with imiquimod has not been established. Typical regimens involve once daily application on either consecutive or alternating days. In our own practice, we have found it most useful to titrate the dose until a clinical response which manifests as an irritant "cytokine" dermatitis becomes apparent. To some degree this dosing interval depends on the anatomic site (eyelid versus back) and the nature of the lesion being treated (hyperkeratotic versus eroded). Consequentially we have found that most patients will require daily application rather than

Table 3 Topical 5-Aminolevulinic Acid PDT in the Treatment of Actinic Keratosis

Reference	No. of Lesions Treated	Light Source	Clearance Rate
Kennedy et al[43]	10	Slide projector light	90% at 18 months
Calzavara-Pinton et al[47]	50	Argon pumped dye laser (630 nm)	84% at 24-36 months
Fink-Puches et al[48]	251	Slide projector light	71% to 36 months
Jeffes et al[49]	218	Argon pumped dye laser (630 nm)	91% (facial lesions), 45% (trunk and extremities) at 8 weeks
Jeffes et al[50]	70	Blue light (417 nm)	66% at 8 weeks

alternating daily application of imiquimod to achieve maximal clinical response. In most instances, we recommend imiquimod cream be applied daily without occlusion from Monday to Friday with a 2-day rest period given over weekends. Delicate areas such as the eyelid are treated TIW for 6 to 8 weeks (Fig. 2A and B). Patients are typically given a follow-up appointment in 2 weeks, at which time their response to therapy is first assessed. In patients with only a minimal-to-mild response to imquimod, occlusion of the treatment site with polyethylene wrap can be used to enhance cutaneous absorption and possibly improve the clinical response. While an exact length of therapy for NMSC treatment has not been established, regimens ranging from 8 to 16 weeks are most often reported.[21-28] Smith and coworkers showed positive results combining 5% fluorouracil and imiquimod in treating renal transplant patients with squamous cell carcinoma in situ.[29] Provocative concepts such as combining multiple topical agents into "therapeutic cocktails" in the hope of achieving synergistic effects clearly requires further exploration.

Future applications of this immune response modulator may include preoperative application to large superficial BCC, SCC in situ, and possibly extra-mammary Paget's disease for chemical highlighting of indistinct margins and possible presurgical debulking. It may also play a role in postoperative treatment where residual actinic or superficial BCC is observed in tissue specimens.

Imiquimod is unique in its ability to modulate immune function. Higher potency formulations, newer applications and indications, and varied formulations can be anticipated.

Photodynamic Therapy

Photodynamic therapy (PDT) is a decades old treatment that has recently been resurrected with applications for dermatologists. PDT describes a two-part method in which a photosensitive drug, light of a specific wavelength, and molecular oxygen combine to produce a therapeutic, tumor-killing effect.[30,31] The light source is chosen such that it matches the absorption spectrum of the photosensitizing agent. Once activated by light, the photosensitized compound reacts with molecular oxygen (O_2) to form highly destructive singlet oxygen.[32,33] The production of intercellular singlet oxygen quickly leads to irreversible oxidative damage and ultimately results in cell death.[31,32] In addition to direct cytotoxicity, PDT produces local vascular effects including thrombosis and vasoconstriction, which may further contribute to tumor destruction.[32]

The rationale for the use of PDT dates back to the discovery in 1900 that the photosensitive dye acridine orange was capable of killing single-celled organisms in the presence of ambient light.[28,33,34] Subsequent studies established that similar photosensitive compounds could preferentially accumulate in cells with higher metabolic rates, such as those present in various precancerous, cancerous, and hyperproliferative states.[35]

Photodynamic therapy using a hematoporphyrin derivative (HPD) was first described as a treatment for human malignancy in 1978.[36] In subsequent work, the use of HDP was replaced by another chemically related compound, porfimer sodium (Photofrin, Axcan Pharma Inc., Quebec, Canada), which contains a purified mixture of oligomeric porphyrins.[37] In 1995, the FDA approved porfimer sodium for the treatment of refractory esophageal cancer and later for non-small-cell lung cancer and treatment of high-grade dysplasia in patients with Barrett's esophagus.[38] Following intravenous porfimer sodium injection, patients are required to wait an interval of 40 to 50 hours before photoactivation can occur.

Persistent photosensitivity similar to that observed in porphyria is the main side effect associated with systemic PDT. With a serum half-life of over 17 days, patients can remain photosensitive for periods of 30 days or even longer following a single treatment.[38] This has proven particularly problematic as the action spectra for porfimer sodium falls within the visible light range, making sunscreens and other methods which block ultraviolet light but not visible light of little benefit.[38]

Despite these obvious limitations, several dermatologic studies were conducted to assess the potential role of systemic PDT as a treatment for NMSC.[38-42] In a large phase II study in patients with either primary or recurrent BCC, PDT with intravenous porfimer sodium resulted in a CR in 88% of tumors.[40] However, in subsequent follow-up, a high number of recurrences were observed in previous CR lesions occurring on average at 16 months in 18% of all treated lesions and in 44% of nasal tumors.[40] Adverse reactions from the systemically administered porphyrin were typical and included persistent photosensitivity lasting up to 3 months, moderate pain, and local edema.

With continued interest in PDT applications and in an effort to minimize side effects associated with systemic PDT, the concept of topical PDT with ALA, a protoporphyrin precursor, was introduced.[43] Applied topically, ALA is rapidly taken up by keratinocytes where it is converted into proto-

Figure 3 Patient undergoing photoactivation of topical ALA using blue light. (Color version of figure is available online.)

porphyrin IX (PpIX), an endogenous photosensitizing compound used to initiate the photodynamic process.[43,44]

Topical ALA with its subsequent conversion into PpIX has several pharmacologic advantages over systemically administered HPD compounds for use in PDT, including a reduced tissue clearance time and an ability to selectively permeate through abnormal keratin.[45] The kinetics of topical ALA, its penetration, and conversion to PpIX are now better understood. It has been estimated that in order for topical ALA to penetrate to a tissue depth of 2.5 to 3.0 mm, an incubation period of 3 to 15 hours is required.[46] This time interval differs from patient to patient and lesion to lesion, leaving much room for treatment variability and uncertainty.

Perhaps because of their superficial nature, topical ALA-PDT was soon investigated as a potential treatment for AK. In preliminary studies, the optimal concentration of topical ALA was not known and solutions ranged between 10 to 30%.[43,47-50] Photoactivation was accomplished with a variety of laser, fluorescent, and incandescent light sources.[43,47-50] The reported CR rates ranged from 64 to 100% over a 1- to 18-month observation period (Table 3).[43,47-50] Based in part on these results, a FDA sanctioned trial was conducted using a topical ALA 20% solution (Levulan Kerastick, DUSA Pharmaceuticals, Inc., Wilmington, MA) with photoactivation provided by a 417 nm blue light device (BLU-U Light Photodynamic Therapy Illuminator, DUSA Pharmaceuticals, Inc.). The approved treatment consists of application of the photosensitizer to discrete, non-hyperkeratotoic lesions of the face and scalp only. The patient returns in 14 to 18 hours for photoactivation with the blue light device (Fig. 3). Photoactivation occurs for 1000 seconds or approximately 17 minutes.[51] The CR rate ranged from 78% for facial to 50% for scalp AK in patients who received one or two topical ALA PDT treatments during a 12-week observation period.[51] These treatment responses compare favorably with other available AK treatments.

Although generally well tolerated, PDT therapy of AK can produce an intense inflammatory response with much discomfort, an observation seen especially in patients with extensive photodamage such as organ transplant recipients. In these patients, subjective complaints of pain and pruritus may begin within minutes of exposure to the blue light and may necessitate premature treatment discontinuation. It is therefore imperative to discuss potential side effects and to provide close monitoring throughout the photoactivation session.

PDT has several potential advantages over other topical therapies for AK including a shorter treatment duration (1000 seconds or less), assured patient compliance, and the potential benefit of reducing other visible signs of photodamage.[52] Disadvantages include the need for "application" and "activation" visits with their necessary monitoring, diminished efficacy on hypertrophic lesions, questionable ability to treat subclinical disease, and potential treatment discomfort.

In addition to its peak absorption at 410 nm (the Soret band), ALA also has significant absorption at 505, 540, 580, and 630 nm. This has naturally lead to attempts to activate ALA using other "off-label" light sources. Many lasers and intense pulsed light (IPL) systems make these wavelengths available. Preliminary studies have successfully shown both the 595-nm-long pulsed dye laser and IPL used in conjunction with ALA to be effective in AK management.[53,54] In addition to requiring significantly shorter treatment durations when compared with the 417-nm blue light, the longer wave-

Table 4 Topical 5-Aminolevulinic Acid PDT in the Treatment of Superficial Basal Cell Carcinoma

Reference	No. of Lesions Treated	Light Source	Clearance Rate
Kennedy et al[43]	80	Slide projector light	90% at 2-3 months
Calzavara-Pinton et al[47]	23	Argon pumped dye laser (630 nm)	50% at 24-36 months
Cairnduff et al[55]	16	Copper vapor dye laser (630 nm)	88% at 2 months, 50 % at 17 months
Wennburg et al[56]	157	Filtered Xenon lamp	92% at 6 months
Soler et al[57]	245	Copper vapor laser and broad band halogen lamp	86% (laser), 82% (halogen) at 6 months

Table 5 Topical 5-Aminolevulinic Acid PDT in the Treatment of Squamous Cell Carcinoma In Situ

Reference	No. of Lesions Treated	Light Source	Clearance Rate
Calzavara-Pinton et al[47]	6	Argon pumped dye laser (630 nm)	100% at 24-36 months
Cairnduff et al[55]	36	Copper vapor dye laser (630 nm)	97% at 2 months, 89% at 17 months
Wennberg et al[56]	18	Filtered xenon lamp	78% at 6 months
Morton et al[58]	85	Xenon short arc lamp	88-92%

lengths are associated with deeper cutaneous penetration and possible increased efficacy.[53] These authors have alternatively used the 595-nm-long pulsed dye laser with its epidermal cooling device (Vbeam, Candela Corp., Wayland, MA) to activate ALA when treating verrucae and other lesions. The short treatment time and cooling device are very acceptable.

The absolute ALA contact duration necessary for topical PDT is uncertain. Several authors have examined the effects of shortening the 14- to 18-hour incubation period. Smith and coworkers found an exposure time of 1 hour with topical ALA before blue light activation to be equally effective as 5-FU for treating AK.[53] In our own experience, for the treatment of refractory verrucae with topical ALA-PDT, a 2- to 4-hour incubation under occlusion yields satisfactory results and is convenient for patients.

In other applications for the treatment of superficial BCC and SCC in situ, short-term (<12 months) CR rates in excess of 90% have been routinely reported with topical ALA-PDT (Tables 4 and 5).[43,47,55-58] However, during more substantive follow-up periods, recurrence rates as high as 32% for superficial BCC and up to 50% for SCC in situ have been documented.[59] Furthermore, this propensity toward having higher tumor recurrences following topical ALA-PDT has been recently demonstrated in both phase II and III FDA studies using a related topical photosensitizing compound, methyl aminolevulinate (MAL) cream (Metvix, Photocure ASA, Oslo, Norway) for the treatment of both superficial and nodular BCC.[60] MAL-PDT with subsequent red light photoactivation (Aktilite, Photocure ASA) was deemed approvable by the FDA for the treatment of actinic keratosis in 2002, though to this date it has not been marketed. However, in trials for both superficial and nodular BCC, the 2-year recurrence rate following topical MAL-PDT was 28% for phase II and as high as 34% in phase III studies.[60,61] Based on this data, the Dermatologic and Ophthalmic Drugs Advisory Committee, which issues recommendations to the FDA, rejected the application for MAL-PDT as a treatment for primary nodular BCC.[61]

In summary, topical ALA-PDT may be considered a first-line treatment for AK. Although the only FDA-approved indication for topical ALA-PDT calls for the treatment of discrete, nonhyperkeratotic AK, recent reports suggest similar results can be obtained when it is used to "paint" larger areas of sun-damaged skin.[62] Photoactivation may be achieved by blue light, various laser, or IPL sources. Because of the higher reported recurrence rates in FDA trials with MAL-PDT, topical ALA-PDT should at best be considered a second-line treatment for both superficial BCC and SCC in situ. The authors do not consider topical ALA-PDT an appropriate treatment option for invasive tumors. Accordingly, we would limit its use to patients who refuse conventional surgical treatments and in whom more effective, better established, nonsurgical approaches such as topical fluorouracil cream, cryotherapy, and radiotherapy are not possible. Other potential treatment scenarios may include patients with multiple tumors, including those with Basal Cell Nevus Syndrome, organ transplant recipients, and compassionate use protocols. Although the FDA-approved ALA incubation period before photoactivation is 14 to 18 hours, several studies suggest that exposure intervals ranging from 1 to 3 hours may be equally effective in the treatment of AK. It is likely that optimal treatment parameters and indications will be forthcoming.

Summary

Dermatologists will continue to face the NMSC epidemic head on. It is compelling to believe that NMSC and its precursors may one day be managed with topical pharmacologic agents alone. At present there are several well-accepted therapeutics for treating AK. Of these, only 5% fluorouracil is currently approved for superficial BCC. Newer agents, such as imiquimod and ALA-PDT, promise additional, effective, nonsurgical alternatives to managing patients with NMSC.

References

1. Cockerill CJ: Histopathology of incipient intarepidermal squamous cell carcinoma ("actinic keratosis"). J Am Acad Dermatol 42:S11-S17, 2000
2. Ashton KJ, Weinstein SR, Maguire DJ, Griffiths LR: Chromosomal aberrations in squamous cell carcinoma and solar keratosis revealed by genomic hybridization. Arch Dermatol 139(7):876-882, 2003
3. Wikonkal NM, Brash DE: Ultraviolet radiation induced signature mutations in photocarcinogenesis. J Investig Dermatol Symp Proc 4(1):6-10, 1999
4. Brash DE, Zeigler A, Jonason AS, Simon JA, Kunala S, Leffell DJ: Sunlight and sunburn in human skin: p53, apoptosis and tumor promotion. J Investig Dermatol Symp Proc 19(2):136-142, 1996
5. Stanimirovic A, Cupic H, Bosnjak B, Kruslin B, Belicza A: Expression of p53, bcl-2 and growth hormone receptor in actinic keratosis, hypertrophic type. Arch Dermatol Res 295(3):102-108, 2003
6. Mittelbronn MA, Mullins DL, Ramos-Caro PA, Flowers FP: Frequency of pre existing actinic keratosis in squamous cell carcinoma. Int J Dermatol 37:677-681, 1998
7. English D, Armstrong B, Kricker A, Winter MG, Heenan PJ, Randall PL: Demographic characteristics, pigmentary and cutaneous risk factors for

squamous cell carcinoma of the skin: a case control study. Int J Cancer 76(5):628-634, 1998
8. Marks R, Rennie G, Selwood T: The relationship of basal and squamous cell carcinomas to solar keratoses. Arch Dermatol 124(7):1039-1042, 1988
9. Goldberg LH, Chang JR, Bauer SC, Schmidt JD: Proliferative actinic keratosis: three representative cases. J Dermatol Surg 26(1):65-69, 2000
10. Feldman SR, Fleischer AB Jr, Williford PM, Jorizzo JL: Destructive procedures are the standard of care for the treatment of actinic keratoses. J AM Acad Dermatol 40(1):43-47, 1999
11. Epstein E: Does intermittent "pulse" topical 5-fluorouracil therapy allow destruction of actinic keratoses without significant inflammation? J Acad Dermatol 38:77-80, 1998
12. Pearlman DL: Weekly pulse dosing: effective and comfortable topical 5-fluorouracil treatment of multiple facial actinic keratoses. J Am Acad Dermatol 25:665-667, 1991
13. Marrero GM, Katz BE: The new fluor-hydroxy peel. A combination of 5-fluorouracil and glycolic acid. Dermatol Surg 24(9):973-978, 1998
14. Loven K, Stein L, Furst K, Levy S: Evaluation of the efficacy and tolerability of 0.5% fluorouracil cream and 5% fluorouracil cream applied to each side of the face in patients with actinic keratosis. Clin Ther 24(6): 990-1000, 2002
15. Welch ML, Grabski WJ, McCollough ML, Skelton HG, Smith KJ, Menon, et al: 5-fluorouracil iontophoretic therapy for Bowen's disease. J Am Acad Dermatol 36(6):956-958, 1997
16. Bargman H, Hochman J: Topical treatment of Bowen's disease with 5-florouracil. J Cutan Med Surg 7(2):101-105, 2003
17. Romadgosa R, Saap L, Givens M, Salverroy A, He JL, Hsia SL et al: A pilot study to evaluate the treatment of basal cell carcinoma with 5-fluorouracil using phosphatidyl choline as a trans-epidermal carrier. Dermatol Surg 26(4):338-340, 2003
18. Buckman SY, Gresham A, Hale P, Hruza G, Anast J, Masferrer J, et al: COX-2 expression is induced by UVB exposure in human skin: implications for the development of skin cancer. Carcinogenesis 19(5):723-729, 1998
19. Arany I, Tyring SK, Brysk MM, Stanley MA, Tomai MA, Miller RL, et al: Correlation between pretreatment levels of interferon response genes and clinical responses to an immune immune response modifier (Imiquimod) in genital warts. Antimicrob Agents Chemother 44(7):1869-1873, 2000
20. Salasche SJ, Levine N, Morrison L: Cycle therapy of actinic keratoses of the face and scalp with 5% topical Imiquimod cream: an open label trial. J Am Acad Dermatol 47(4):571-577, 2002
21. Kagy MK, Amonette R: The use of imiquimod 5% cream for the treatment of superficial basal cell carcinomas in a basal cell nevus syndrome patient. Dermatol Surg. 26:577-578, 2000
22. Beutner KR, Geisse JK, Helman D, Fox TL, Ginkel A, Owens ML: Therapeutic response of basal cell carcinoma to the immune response modifier imiquimod 5% cream. J Am Acad Dermatol. 41:1002-1007, 1999
23. Schroeder TL, Sengelmann RD: Squamous cell carcinoma in situ of the penis successfully treated with imiquimod 5% cream. J Am Acad Dermatol 46:545-548, 2002
24. Chen K, Shumack S: Treatment of Bowen's disease using a cycle regimen of imiquimod 5% cream. Clin Exp Dermatol 28S:10-12, 2003
25. Nagore E, Sevila A, Sanmartin O, Botella-Estrada R, Requena C, Serra-Guillen C, Sanchez-Pedreno P, Guillen C: Excellent response of basal cell carcinomas and pigmentary changes in xeroderma pigmentosum to imiquimod 5% cream. Br J Dermatol 149:858-861, 2003
26. Shumack S, Robinson J, Kossard S, Golitz L, Greenway H, Schroeter A, Andres K, Amies M, Owens M: Efficacy of topical 5% imiquimod cream for the treatment of nodular basal cell carcinoma: comparison of dosing regimens. Arch Dermatol 138:1165-1171, 2002
27. Huber A, Huber JD, Skinner RB, Kuwahara RT, Haque R, Amonette RA: Topical imiquimod treatment for nodular Basal cell carcinomas: an open-label series. Dermatol Surg 30:429-430, 2004
28. Mackenzie-Wood A, Kossard S, de Launey J, Wilkinson B, Owens ML: Imiquimod 5% cream in the treatment of Bowen's disease. J Am Acad Dermatol 44:462-470, 2001
29. Smith KJ, Germain M, Skelton HG: Squamous cell carcinoma in situ (Bowen's disease) in renal transplant patients treated with 5% imiquimod and 5% 5-fluorouracil therapy. Dermatol Surg 27(6):5611-5614, 2001
30. Moan J, Peng Q: An outline of the hundred-year history of PDT. Anticancer Res 23:3591-3600, 2003
31. Levy JG: Photosensitizers in photodynamic therapy. Semin Oncol. 6:4-10, 1994
32. Szeimies RM, Landthaler M: Photodynamic therapy and fluorescence diagnosis of skin cancers. Recent Results Cancer Res 160:240-245, 2002
33. Taub AF: Photodynamic therapy in dermatology: history and horizons. J Drugs Dermatol 3:S8-25, 2004
34. von Tappeiner H, Jesionek A: Therapeutische Verusche mit fluorescierenden Stoffen. Munch Med Wochenschr 47:2043-2044
35. Dougherty TJ: Photosensitization of malignant tumors. Semin Surg Oncol 2:24-37, 1986
36. Dougherty TJ, Kaufman JE, Goldfarb A, Weishaupt KR, Boyle D, Mittleman A: Photoradiation therapy for the treatment of malignant tumors. Cancer Res. 38:2628-2635, 1978
37. Liu H: Photodynamic therapy in dermatology with porfimer sodium and benzoporphyrin derivative: an update. Semin Oncol 6:11-14, 1994
38. Axcan Pharama Inc Website: http://www.scandipharm.com/en-us/photofrin_faq.aspx?lang=en-us&m=120&n=4#676. Accessed on February 29, 2004
39. Schweitzer VG: PHOTOFRI. N-mediated photodynamic therapy for treatment of early stage oral cavity and laryngeal malignancies. Lasers Surg Med 29(4):305-313, 2001
40. Wilson BD, Mang TS, Stoll H, Jones C, Cooper M, Dougherty TJ: Photodynamic therapy for the treatment of basal cell carcinoma. Arch Dermatol 128:1597-1601, 1992
41. Allison RR, Mang TS, Wilson BD: Photodynamic therapy for the treatment of nonmelanomatous cutaneous malignancies. Semin Cutan Med Surg 17(Jun):153-163, 1998
42. Schweitzer VG: Photofrin-mediated photodynamic therapy for treatment of aggressive head and neck nonmelanomatous skin tumors in elderly patients. Laryngoscope 111:1091-1098, 2001
43. Kennedy JC, Pottier RH, Pross DC: Photodynamic therapy with endogenous protoporphyrin IX: basic principles and present clinical experience. J Photochem Photobiol B 6:143-148, 1990
44. Ratcliffe SL, Matthews EK: Modification of the photodynamic action of delta-aminolaevulinic acid (ALA) on rat pancreatoma cells by mitochondrial benzodiazepine receptor ligands. Br J Cancer 71: 300-305, 1995
45. Tsai JC, Chen IH, Wong TW, Lo YL: In vitro/in vivo correlations between transdermal delivery of 5-aminolaevulinic acid and cutaneous protoporphyrin IX accumulation and effect of formulation. Br J Dermatol 146:853-862, 2002
46. Taub AF: Photodynamic therapy in dermatology: history and horizons. J Drugs Dermatol 3:S8-25, 2004
47. Calzavara-Pinton PG: Repetitive photodynamic therapy with topical delta-aminolaevulinic acid as an appropriate approach to the routine treatment of superficial non-melanoma skin tumours. J Photochem Photobiol B 29:53-57, 1995
48. Fink-Puches R, Hofer A, Smolle J, Kerl H, Wolf P: Primary clinical response and long-term follow-up of solar keratoses treated with topically applied 5-aminolevulinic acid and irradiation by different wave bands of light. J Photochem Photobiol B 41:145-151, 1997
49. Jeffes EW, McCullough JL, Weinstein GD, Fergin PE, Nelson JS, Shull TF, Simpson KR, Bukaty LM, Hoffman WL, Fong NL: Photodynamic therapy of actinic keratosis with topical 5-aminolevulinic acid. A pilot dose-ranging study. Arch Dermatol 133:727-732, 1997
50. Jeffes EW, McCullough JL, Weinstein GD, Kaplan R, Glazer SD, Taylor JR: Photodynamic therapy of actinic keratoses with topical aminolevulinic acid hydrochloride and fluorescent blue light. J Am Acad Dermatol. 45:96-104, 2001
51. Piacquadio DJ, Chen DM, Farber HF, Fowler JF Jr, Glazer SD, Goodman JJ, Hruza LL, Jeffes, EW, Ling MR, Phillips TJ, Rallis TM, Scher RK,

Taylor CR, Weinstein GD: 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 140(Jan):41-46, 2004

52. 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 140(1):33-40, 2004
53. Alexiades-Armenakas MR, Geronemus RG: Laser-mediated photodynamic therapy of actinic keratoses. Arch Dermatol 139:1313-1320, 2003
54. Ruiz-Rodriguez R, Sanz-Sanchez T, Cordoba S: Photodynamic photorejuvenation. Dermatol Surg 28:742-744, 2002
55. Cairnduff F, Stringer MR, Hudson EJ, Ash DV, Brown SB: Superficial photodynamic therapy with topical 5-aminolaevulinic acid for superficial primary and secondary skin cancer. Br J Cancer 69:605-608, 1994
56. Wennberg AM, Lindholm LE, Alpsten M, Larko O: Treatment of superficial basal cell carcinomas using topically applied delta-aminolaevulinic acid and a filtered xenon lamp. Arch Dermatol Res 288:561-564, 1996
57. Soler AM, Angell-Petersen E, Warloe T, Tausjo J, Steen HB, Moan J, Giercksky KE: Photodynamic therapy of superficial basal cell carcinoma with 5-aminolevulinic acid with dimethylsulfoxide and ethylendiaminetetraacetic acid: a comparison of two light sources. Photochem Photobiol 71(Jun):724-729, 2000
58. Morton CA, Whitehurst C, McColl JH, Moore JV, MacKie RM: Photodynamic therapy for large or multiple patches of Bowen disease and basal cell carcinoma. Arch Dermatol 137(Mar):319-324, 2001
59. Marmur ES, Schmults CD, Goldberg DJ: A review of laser and photodynamic therapy for the treatment of nonmelanoma skin cancer. Dermatol Surg 30:264-271, 2004 (Suppl. 2)
60. FDA.gov website. Retrieved on March 13, 2004. http://www.fda.gov/ohrms/dockets/ac/03/slides/1
61. Photocure.com website. Retrieved on March 13, 2004. http://www.photocure.com/
62. Smith S, Piacquadio D, Morhenn V, Atkin D, Fitzpatrick R: Short incubation PDT versus 5-FU in treating actinic keratoses. J Drugs Dermatol 2:629-635, 2003
63. Geisse JK, Rich P, Pandya A, Gross K, Andres K, Ginkel A, Owens M: Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: a double-blind, randomized, vehicle-controlled study. J Am Acad Dermatol 47:390-398, 2002