CLINICAL INVESTIGATION

Emerging medical treatments for actinic keratoses, squamous cell carcinoma and basal cell carcinoma

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Skin cancer is the most common cancer in the USA. Non-melanoma skin cancers, which include basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), comprise the majority. BCC and SCC are commonly treated with surgical excision, curettage, cryotherapy and radiation. Actinic keratoses (AK) are considered precursors of SCC and are commonly treated with 5-fluorouracil, imiquimod, diclofenac, liquid nitrogen or photodynamic therapy. On 5 March 2012 we conducted a Medline search for Phase II and III trials of novel medical treatments that have been reported within the last 3 years. We also searched clinicaltrials.gov to find promising treatments in development. Ingenol mebutate has been investigated as a treatment for AK, SCC and BCC. Dobesilate and the combination of 5-fluorouracil and salicylic acid were also studied for AK. Cetuximab, an EGF receptor inhibitor, was studied for SCC; and vismodegib, a Hedgehog inhibitor, was studied for BCC.

Keywords: 5-fluorouracil/salicyclic acid • actinic keratosis • basal cell carcinoma • celecoxib • cetuximab • dobesilate • ingenol mebutate • squamous cell carcinoma • vismodegib

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Skin cancer is the most prevalent malignancy in the USA. More than 3.5 million skin cancers in over two million people are diagnosed annually [1]. Non-melanoma skin cancer composes the majority of cutaneous malignancies.

Basal cell carcinoma (BCC) is the most common form of skin cancer; an estimated 2.8 million are diagnosed annually in the USA [1]. Significant risk factors for BCC include exposure to UV radiation and genetic predisposition [2]. BCC tends to occur in areas of chronic sun exposure, and approximately 74% of cases occur on the head and neck [3]. Worldwide incidence ranges from 407 per 100,000 white men and 212 per 100,000 white women in the USA to two per 100 in certain regions of Australia [4].

BCC was previously thought to arise from multipotent stem cells residing in a specialized part of the hair follicle called the bulge. However, recent evidence suggests that BCC actually arises from long-term resident progenitor cells of the interfollicular epidermis and the upper infundibulum [5]. Although BCC rarely metastasizes, significant morbidity in the form of local tissue destruction and disfigurement can occur [6]. The tumor has the capacity to invade and destroy tissue around it, including healthy skin, nerves, lymphatic and blood vessels, cartilage and bone [7]. Disfigurement may occur if the tumor is left untreated or incompletely removed.

Squamous cell carcinoma (SCC) is the second most common form of skin cancer, with an estimated 700,000 cases diagnosed each year in the USA [1]. Risk factors that apply to SCC include fair skin, excessive cumulative exposure to UV radiation, advancing age, outdoor vocation or recreation, and living in 'sun belt' latitudes [8]. The highest risk factors for the development of SCC are the

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presence of actinic keratoses (AK) or previous non-melanoma skin cancer [9], although SCC may also arise from leukoplakia, radiation AK, scars, chronic ulcers or *de novo*. In the USA, the annual age-adjusted incidence for SCC is eight to 135 per 100,000 white men per year, and 26–59 per 100,000 white women per year [10].

AK is a common precancerous skin lesion that develops as a result of chronic UV irradiation. AK most commonly affects individuals of Fitzpatrick skin type I or II and is predominately found on sun-exposed areas such as the face, bald scalp, ears and lateral forearms [11]. Frequency of AK correlates with cumulative UV exposure; therefore, age is an important factor in the development of AK [8]. In Australia, where there is a large proportion of Caucasians with Fitzpatrick skin types 1 and 2, AK and SCC combined have an estimated prevalence of 40 to 50% of the population aged 40 years and older [8]. AK can occur at younger ages in men, likely because of more occupational and recreational exposure. Recent data from the National Ambulatory Medical Care Survey from 1996 to 2005 showed that 58.9% of patients presenting with AK were male, 98.8% were white and approximately 30% were aged 70–79 years [12].

AK are the third most common reason for consulting a dermatologist [8]. It has been described along the spectrum of carcinoma *in situ* involving proliferation of atypical keratinocytes within the epidermis only [12,13]. AK usually present as scaly lesions, typically 2–6 mm in diameter and are more easily felt than seen [14]. The lesion typically develops on areas of the skin exposed to the sun and commonly present as a red, scaling papule or plaque [15]. Subclinical lesions can be found nearby to clinically obvious ones and may be part of a field of cancerization [16]. Studies of the literature have shown that the risk of progression of a single AK to invasive SCC ranges from 0.25 to 20% per year [17]. Up to 60% of invasive SCC arises from AK [18]. Cumulative risk depends on the total number of lesions and the length of time they are present. One study has shown that people with more than ten AKs had a 14% cumulative probability of developing SCC within 5 years [19].

Similar to AK, SCC is usually found in areas that receive heavy UV radiation, such as the face, scalp, neck and ears. SCC may present as sharply defined, red scaling plaques [20], enlarging smooth, firm papules or nodules, or rough and hardened patches. Ulceration may develop as the lesion progresses. When SCC becomes invasive, it tends to become symptomatic with pruritus, tenderness and bleeding upon mild traumatization [21].

SCC grows rapidly by expanding along tissue planes and results in tissue destruction. It may penetrate the basement membrane to invade the dermis. SCC has an alarming potential to metastasize to regional and distant sites. Qualities of SCC that make it more likely to metastasize are rapid growth to larger than 2 cm, 6 mm depth of invasion, previously treated tumors or tumors located on high-risk areas such as the nose, ear or lip [8]. SCC of the lip or ear metastasizes at rates that range from 10 to 25% [22]. SCC that recurs locally metastasizes at a rate of 25% for most cutaneous lesions and 30–45% for ear and lip tumors [22]. Metastatic disease has a poor prognosis with 10-year survival rates of 20% for regional lymph node involvement and less than 10% for patients with distant metastasis [14]. However, patients with primary cutaneous SCC have an excellent prognosis with low risk of metastasis if treated appropriately. Current treatments can eliminate up to 90% of local tumors [14].

Current treatments for AK & SCC

Treatments for AK can be divided into two categories: lesion-directed therapy and field-directed therapy. In the past, lesion-directed therapy was the standard of care. Today, with greater insight into the relationship between AK and SCC and the awareness that clinical and subclinical AKs frequently co-exist in a field, field-directed therapies have become an important aspect of therapy [23].

Lesion-directed treatments include surgical excision, curettage, cryotherapy and lasers [24]. Curettage is an option when a sample of tissue is required for histological analysis in order to detect local invasion. However, it also requires local anesthesia and may result in scarring [25,26]. Cryotherapy is another option for treating AK. Although it is quick and easy to perform, it does not allow for histological examination of tissue. Lesions response rates range from 75 to 98% [27]. Side effects include blistering, dyspigmentation and pain [28]. Laser ablation offers the option of treating single lesions or resurfacing an entire field [29]. The most commonly used ablative lasers are CO_2 and Er:YAG [25]. Remission is achieved for 90–91% of AKs. Single lesion recurrence rates range from 10 to 15% between 3 and 6 months [24]. Disadvantages of laser therapy include being strongly user-dependant and costly. It can cause inflammation, dyspigmentation, scarring and pain [23,27].

Field-directed therapy offers the advantages of being noninvasive and most treatments can be administered by the patient. However, some treatments require long and complex schedules that adversely effect patient compliance. Unlike lesion-directed methods, field-directed methods are able to target subclinical AKs.

US FDA-approved options include photodynamic therapy (PDT), imiquimod 5% cream, diclofenac 3% in hyaluronic acid (HA) gel, and topical 5-fluorouracil (5-Fu) in varying strengths.

PDT is a combination of a locally applied photosensitizing agent and a red light [30]. Methyl aminolevulanate (MAL) or 5-aminolevulinic acid (ALA) act as precursors of photosensitizers and are preferentially taken up by rapidly dividing atypical keratinocytes. Subsequent application of red light leads to the formation of reactive oxygen species that destroy the cells. Single-treatment sessions demonstrate response rates ranging from 70 to 78%. When treated with two sessions 1 week apart, the response rate is 90% [23,28,31]. A major disadvantage is that PDT can be painful and causes hypersensitivity to daylight [27].

Imiquimod is a topical immunomodulating drug that acts as a Toll-like receptor 7 (TLR7) agonist. TLR7 is involved in signaling pathways that ultimately result in the release of inflammatory cytokines such as TNF-α, IFN-α and IL-2. By activating TLR7, imiquimod induces the cell-mediated immune response and causes destruction of atypical keratinocytes [32,33]. Its mechanism of action is highly specific for neoplastic cells and subclinical lesions are readily highlighted by the inflammatory reaction [34]. It is available in 5, 3.75 and 2.75% formulations. When imiquimod 5% is applied to AK twice a week for 16 weeks, it can induce complete remission in 84% of lesions. However, 10% recur in 1 year and 20% recur in 2 years. It can cause a mild-to-moderate local reaction involving erythema, itching or burning [23,32]. Imiquimod 3.75 and 2.5% formulations have been tested in daily dosing regimens [35]. The creams were applied in two 2-week treatment cycles separated by a 2-week, no-treatment interval. Complete and partial clearance rates (defined as ≥75% lesion reduction) were 6.3 and 22.6% for placebo, 30.6 and 48.1% for imiquimod 2.5%, and 35.6 and 59.4% for imiquimod 3.75%, respectively ($p < 0.001$ vs placebo, each; $p = 0.047$, 3.75 vs 2.5% for partial clearance) [35]. Imiquimod 3.75% cream exhibits lower efficacy than the 5% cream when applied three-times a week for 16 weeks or for two 4-week cycles with a 4-week no-treatment interval [36]. The efficacy is similar to imiquimod 5% when compared with a twice-weekly schedule for 16 weeks. Adverse effects are also similar to imiquimod 5% [36]. Another FDA-approved field-directed treatment for AK is diclofenac 3% in 2.5% HA gel (diclofenac/HA). Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) that inhibits cyclooxygenases (COX). COX-2 is involved in the production of PGE2, a cytokine that promotes proliferation of T and B cells and has angiogenic properties [23]. The mechanism of action of diclofenac may ultimately involve the induction of apoptosis in tumorigenic cells [37]. It is applied with HA in order to increase its local bioavailability. When applied twice-daily for 3 months, complete clinical clearance was achieved in 40% and histopathological clearance was achieved in 30% of patients. When applied twice-daily for 6 months, complete clinical clearance and histopathological clearance were achieved in 45 and 40% of patients, respectively [38]. When the gel is applied twice-daily for 90 days, the response rate is 50%. Although uncommon, side effects include erythema, crusting, scaling and pruritus at the treatment site [23].

Topical 5-FU is the oldest topical treatment for AK. It is a nucleotide that is enzymatically modified inside cells. Once modified, it is able to inhibit DNA synthesis by blocking the methylating activity of thymidylate synthase. Thus, it selectively effects rapidly dividing cells and, therefore, is more specific for neoplastic cells [39]. It is currently available in 5 and 0.5% formulations. In 2010, Kaur *et al.* reviewed the literature to determine the efficacy of the two formulations when used to treat the face and scalp. Nine studies were included in their final analysis [40]. For 0.5% 5-Fu, complete clearance rates were 14.9 and 57.8% when examined after 1 and 4 weeks of treatment, respectively. A dose of 5% 5-FU demonstrated complete clinical clearance in 43 and 100% after 4 and 2 weeks of treatment, respectively [40]. It is associated with severe local reactions that include pain, erythema, crusting, dyspigmentation, ulceration and scarring and, therefore, is not a preferred first-line treatment [41]. Chemical peels are also used in the treatment of AK. They stimulate new skin growth by creating an injury to a specific depth of skin [42]. Studies of a medium-depth peel consisting of Jessner's solution and 35% trichloro-acetic acid in the treatment of AK demonstrated a reduction in the number of visible AK by 75% [42,43]. Side-effects of peels include burning, irritation and erythema. Medium-depth peels can create lines of demarcation that are technique-related [42].

Unlike AK, the first-line treatment for non-metastatic SCC is surgical excision because of its advanced nature. The vast majority of tumors are radiosensitive and radiation is an option for inoperable tumors and for patients who are not surgical candidates. For small low-risk lesions, curettage is an option. Topical treatments overlap with AK and include 5-Fu, imiquimod, laser therapy and PDT [21].

Emerging treatments for AK & SCC

- **Ingenol mebutate**

The sap of *Euphorbia peplus* has a long history of anecdotal use in treating a variety of disorders including warts, corns and skin cancers, as well as neoplasias of stomach, liver and uterus (Table 1) [44]. Serial fractionations of *E. peplus* sap has isolated an actively cytotoxic macrocytic diterpene, PEP-005, now known as ingenol mebutate [45].

Current treatments for AK act through either cytotoxic or immunomodulating mechanisms. Ingenol mebutate is unique because it likely acts through both mechanisms, which may be the reason it works after only 2 to 3 days of treatment [46]. It has been proposed that it works in two phases – an acute necrolytic phase and a delayed inflammatory phase [46]. *In vitro* models have demonstrated that rapid necrosis is mediated by the dissipation of mitochondrial cell membrane potentials. The subsequent decrease in adenosine triphosphate production leads to cell death. The exact process by which ingenol mebutate initiates this process is still under debate, but it may dissolve in the plasma membrane and form vesicles from which Ca^{2+} is released into the intracellular environment. A rise in intracellular Ca^{2+} undermines the integrity of mitochondrial membranes and causes cell necrosis within 1 h. The second phase is believed to be mediated by B cells and neutrophils. Necrotic cells release proinflammatory cytokines that stimulate B-cell maturation and production of tumor cell-specific antibodies via PKC. In addition, cytokines lead to the upregulation of endothelial adhesion molecules. Neutrophils migrate to the region and react with antigen–antibody complexes on dysplastic keratinocytes and release reactive oxygen species. This inflammatory response peaks in approximately 24 h and resolves in 5–10 days [45,46].

Siller *et al.* conducted a multicenter, randomized, double-blind, vehicle-controlled, Phase IIa study of the safety and efficacy of ingenol mebutate as a treatment for AK [47]. A total of 58 patients who had at least five biopsy-proven AKs (total number of lesions = 285) were treated with ingenol mebutate gel 0.0025, 0.01 or 0.05% twice, either on days 1 and 2 or on days 1 and 8. Both treatment schedules and all concentrations were well tolerated. Only local skin

Table 1. Clinical trials of treatments for actinic keratoses completed between 2009 and 2012.

Treatment	Number of patients	Results	Most common adverse effects	Authors (Year)	Ref.
Ingenol mebutate – gel concentrations of 0.0025, 0.01 or 0.05% applied twice, either on days 1 and 2 or on days 1 and 8	58 (285 lesions)	0.05% gel: complete clearance in 75% of lesions, 80% decrease in number of lesions in 67% of patients	Well tolerated; erythema, flaking, scaling, dryness and scabbing, crusting	Siller *et al.* (2009)	[47]
Ingenol mebutate – 0.025% gel applied once-daily for 3 days and 0.05% gel applied once-daily for 2 or 3 days	222	Complete clearance from 40.0–54.4%; partial clearance from 56.0–75.4%	Erythema, flaking, scaling and crusting	Anderson *et al.* (2009)	[49]
Ingenol mebutate – 0.025% gel applied once-daily to face/scalp for 3 days or 0.05% gel applied to trunk/extremities for 2 days	1005	Head/scalp: complete clearance 42.2%; partial clearance 63.9%; trunk/extremities: complete clearance 34.1%; partial clearance 49.1%	Erythema, flaking, scaling, crusting, swelling, vesiculation/pustulation and erosion/ulceration	Lebwohl *et al.* (2012)	[50]
Dobelisate – 5% cream applied twice-daily for 16 weeks	30	Complete clearance in 70%; partial response in 20%	Pruritus and stinging	Cuevas *et al.* (2011)	[51]
0.5% 5-Fu/10% SA – solution applied daily versus diclofenac HA twice-daily for maximum 12 weeks	470	Histologic clearance: 5-Fu/SA 72%; diclofenac HA 59.1%	Inflammation and burning	Stockfleth *et al.* (2011)	[26]
PDT with BF-200 ALA – nanoemulsion gel with 7.8% ALA versus PDT-MAL and PDT-placebo	600	Patient complete clearance: BF-ALA 78.2%, MAL 64.2%, placebo 17.1%; lesion complete clearance: BF-ALA 90.4%, placebo 37.1%	Erythema, burning and pain	Dirschka *et al.* (2012)	[57]
PDT with ALA patch versus PDT-placebo patch and cryotherapy	449	Lesion clearance: 82–89% ALA patch, 29–29% placebo patch, 77% cryosurgery	Erythema, burning and pain	Hauschild *et al.* (2009)	[58]

5-Fu: 5-fluorouracil; ALA: 5-aminolevulinic acid; HA: Hyaluronic acid; MAL: Methyl aminolevulanate; PDT: Photodynamic therapy; SA: Salicylic acid .

reactions were reported and included dose-related eythema, flaking, scaling, dryness, scabbing and crusting. These reactions subsided within 1 month and there was no reported scarring or abnormal proliferations. Not surprisingly, 0.05% ingenol mebutate was most efficacious and resulted in complete clinical clearance of 71% of lesions, and 67% of patients experienced clearance of at least 80% of lesions. There was a statistically significant difference between ingenol mebutate 0.05% and vehicle gel with regard to complete clinical clearance ($p < 0.0001$) and in the number of patients who experienced greater than 80% clinical clearance ($p = 0.0185$). There was no statistical difference between the two treatment schedules as far as safety and efficacy [47,48].

Anderson *et al.* conducted a multicenter, randomized, double-blind, vehicle-controlled, Phase IIb study of the efficacy and safety of ingenol mebutate 0.025% applied once-daily for 3 consecutive days and ingenol mebutate 0.05% applied once-daily for 2 or 3 consecutive days [49]. In order to be included, patients must have four to eight typical, visible, discrete lesions within a contiguous 25 cm^2 field. The treatments were applied to an entire field. A total of 222 patients were included in the analyses. All three treatment regiments were significantly more effective than vehicle gel at reducing the number of AKs on day 57. The partial clearance rates of lesions ranged from 56.0 to 75.4% and were dose-related (p ranged from 0.0002 to <0.0001 vs vehicle gel). Similarly, complete clearance ranged from 40.0 to 54.4% (p ranged from 0.0006 to < 0.0001 vs vehicle gel). Local skin reactions included erythema, flaking/scaling and crusting, which peaked between days 3 and 8. These reactions resolved within 2–4 weeks of treatment [49].

The results of a large multicenter, randomized, double-blind, Phase IIb study were recently reported by Lebwohl *et al.* [50]. In patients treated on the face and scalp, 42.2% of patients who received ingenol mebutate experienced complete clearance whereas 3.7% in the vehicle gel group experienced complete clearance ($p < 0.001$). Partial clearance was reported in 63.9% of patients treated with ingenol mebutate and 7.4% of patients treated with vehicle gel ($p < 0.001$). Local skin reactions included erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation and erosion/ulceration. These reactions were graded and added in order to create a composite score that ranged from 0 to 24 (higher numbers indicating more severe reactions). Local reactions peaked on day 4 and decreased by day 8. The mean highest score experienced by an individual using ingenol mebutate was 9.1 ± 4.1, as compared with 1.8 ± 1.6 for the vehicle group. In patients treated on the trunk or extremities, 34.1% treated with ingenol mebutate experienced complete clearance, as compared with 4.7% of patients treated with vehicle gel ($p < 0.001$). Partial clearance was reported for 49.1% of patients treated with ingenol mebutate and 6.9% in the vehicle group ($p < 0.001$). The mean maximum local response score for the ingenol mebutate group was 6.8 ± 3.5, as compared with 1.6 ± 1.5 for the vehicle group. This was the largest clinical study of ingenol mebutate for treatment of AK to date.

Ingenol mebutate was approved by the FDA for the treatment of AK in January 2012. Multiple trials were recently completed that studied the safety and efficacy of ingenol mebutate for the treatment of AK. The results of these studies are yet to be released (clinicaltrials.gov).

Dobesilate

Potassium dobesilate (2,5-dihydroxybenzene sulfonate) is a synthetic molecule that is well established as a safe treatment for diabetic retinopathy and chronic venous insufficiency and has recently been approved as a treatment for psoriasis and rosacea [51]. *In vitro* studies have demonstrated that dobesilate inhibits FGF-1 and VEGF, both of which are powerful promoters of angiogenesis [51,52]. It is believed that the therapeutic effects of dobesilate lie in its antiangiogenic and antiproliferative properties [51].

Cuevas Sanchez *et al.* investigated the efficacy and tolerability of potassium dobesilate 5% cream for the treatment of AK in a prelimary open-label study [53]. A total of 30 patients completed the trial. Patients that were included had at least one AK on the face or scalp. Lesions were compared based on their grades as determined clinically before the start of treatment. Mild, nonhyperkeratotic lesions were deemed grade I (17.4%), moderate lesions were grade II (43.5%) and severe, hyperkeratotic lesions were grade III (39.1%). Potassium dobesilate 5% cream was topically applied to individual AK lesions twice a day for 16 weeks. There was no placebo treatment. At 8 weeks after the end of treatment, potassium dobesilate induced complete clearance in 70% of patients, 20% of patients experienced partial response (PR), defined as 75% reduction in lesions, and 10% showed less than 75% reduction in lesions or no clinical response. The clearance rate according to baseline grade was 100% for grade I lesions, 63.3% for grade II lesions and 64.3% for grade III lesions. These findings are difficult to interpret in the absence of a placebo arm because AK can spontaneously regress. Only local side effects were experienced, and these included mild pruritus (22%) and mild stinging (17%). One patient experienced erythema outside of the treated area at

week 4 with complete disappearance at week 8 [53]. The investigators were the first to study this drug for the treatment of AK. These preliminary results are promising, but no other clinical trials are ongoing.

Low-dose 5-Fu in 10% salicylic acid

As mentioned previously, 5% 5-FU is a long-standing treatment for AK, but its use is limited by the severe local adverse reactions it causes. Low-dose 0.5% 5-Fu has a more tolerable adverse effect profile and both 5% and 0.5% have a clearance rate of 50% when applied once-daily for 4 weeks and twice-daily for 4 weeks, respectively [54]. Recent interest has emerged in treating AK with 0.5% 5-Fu in 10% salicylic acid (5-Fu/SA).

For over 2000 years, SA has been used as a topical treatment for many dermatologic conditions. Today, it is commonly used as a treatment for hyperkeratotic lesions such as warts, calluses, psoriasis and ichthyosis [55]. It is considered a 'keratolytic', but the actual mechanism may involve a decrease in cohesion between corneocytes leading to epidermal cell shedding [55]. One major limitation is that it is easily and rapidly absorbed into the bloodstream following topical application, leading to rare but serious side effects such as hyperventilation, vomiting, confusion, dizziness, delirium, psychosis, stupor and coma [55]. The rationale for using it in a formulation with 5-FU is that AKs exhibit varying degrees of hyperkeratosis, which can interfere with the local absorption of 5-FU [26]. By combining the two drugs, the efficacy of 5-FU may be augmented.

Based on the findings of the pilot study, Stockfleth *et al.* investigated 5-Fu/SA in a multicenter, randomized, double-blind, Phase III study for the treatment of AK [26]. They compared 5-Fu/SA to its vehicle and diclofenac HA. They included 470 patients with four to ten biopsy-proven grade I or II AK on their face or bald scalp. Lesions were considered grade I if mild and more easily felt than seen, or grade II if moderate, thick, hyperkeratotic and easily felt. Patients in the 5-Fu/SA and vehicle control group applied the solution once-daily and patients in the diclofenac HA group applied the treatment twice-daily. Investigators making assessments were not informed of treatment schedules to avoid bias. All patients were instructed to apply respective treatments until the lesions cleared, up to a maximum of 12 weeks. Punch biopsies were performed before and after treatment. This was the first controlled study that examined histological clearance as a primary objective. Biopsy is considered the gold standard for proving efficacy and, therefore, this study was more likely to uncover treatment success. With regard to histologic clearance, 5-Fu/SA demonstrated a rate of 72%, diclofenac HA had a rate of 59.1%, and the vehicle had a rate of 44.8%, and 5-Fu/SA was significantly superior to both ($p < 0.01$ vs diclofenac HA; $p < 0.0001$ vs vehicle). The mean number of lesions per patient before the start of treatment was 5.5. After treatment, the mean number of lesions per patient declined to 2.8 in the 5-Fu/SA group, 3.7 in the vehicle group and 3.2 in the diclofenac HA group ($p < 0.025$ for both treatments vs vehicle). At week 20, lesions were assessed for clinical clearance. The clearance rate in terms of number of lesions was significantly greater for 5-Fu/SA as compared with diclofenac HA and vehicle ($p < 0.001$ for both). At week 6 of treatment, more than 70% of patients using 5-Fu/SA reported little or moderate inflammation and burning and 60% of patients using the vehicle reported burning, and 20% reported inflammation. Only 22% of patients in the diclofenac HA group reported either inflammation or burning. The vehicle contained dimethyl sulfoxide and ethanol, both of which are known to cause irritation [26]. This study demonstrated the superiority of 5-Fu/SA as compared with placebo as well as a current treatment, diclofenac/HA.

A clinical trial is currently underway comparing the efficacy and safety of a solution of 0.5% 5-FU cream and 10% SA compared with cryotherapy in subjects with moderate-to-severe hyperkeratotic AK (clinicaltrials.gov NCT01358851).

Cetuximab

Cetuximab is a monoclonal antibody that inhibits the EGF receptor, which is involved in pathways that favor proliferation of cells and is overexpressed in many epithelial tumors [56]. Cetuximab is currently approved for treatment of SCC of the head and neck and colorectal carcinoma. In 2011, Maubec *et al.* published the results of a multicenter, open-label, uncontrolled Phase II study of the use of cetuximab as monotherapy in patients with unresectable SCC of the skin [56]. Patients were included if they had biopsy-proven SCC with immunohistochemical evidence of strong or moderate EGF receptor expression, locally advanced tumors that were deemed inoperable, or metastases. In total, 31 patients were included. Cetuximab was administered as an initial dose of 400 mg/m^2 by intravenous infusion followed by weekly infusions of 250 to 400 mg/m^2. Treatment continued as long as the tumor demonstrated regression or stayed stable with a median number of treatments of 15 (range of 1 to 47). Disease control rates (defined as complete response [CR], PR or stable disease) at week 6 were 69% (95% CI: 52–84%) in the intention-to-treat population (ITT = patients with missing evaluations considered as treatment failure) and 81% (95% CI: 63–93%) in the perprotocol population (defined as patients treated for at least 6 weeks with tumors capable of being evaluated radiologically). At week 6, the response rate (defined as complete or partial response) for the ITT group was 11% (95% CI: 3–26%) and 13% (95% CI: 4–30%) in the perprotocol group. The mean overall survival in the ITT group was 8.1 months (95% CI: 6.9–9.3 months). Cetuximab allowed for control of disease for 1 year in a patient with a grade T3 tumor and for 8 months in a partial responder with lung metastasis. For the ten patients who experienced CR or PR, the median duration of the response was 6.8 months (95% CI: 4.1–8.3 months). All 36 participants experienced adverse events that were expected based on previously reported studies. The most common adverse reactions included acne-like rash, infection, dry skin, pruritus, nausea/vomiting, varying eye disorders and nail/hand disorders. During the course of the study seven patients died, but the authors believed these deaths were not related to the treatment under investigation. This study demonstrated that cetuximab may be a valuable treatment option for nonresectable SCC, especially in elderly patients who would be ineligible for traditional chemotherapy [56].

PDT with BF-200 ALA & patch

The utility of PDT with ALA in the treatment of AK has been previously discussed. BF-ALA is a nano-emulsion gel that contains 7.8% ALA. This new formulation has improved stability compared with older formulations and allows for greater penetration into the stratum corneum. The potential advantage is the possibility of using a lower concentration of 5-ALA. Dirschka *et al.* conducted a Phase III study comparing the efficacy and safety of BF-200 ALA to 16% MAL cream and placebo [57]. All were administered with the schedule and illumination conditions described on the label for the registered MAL cream. Patient complete clearance was defined as complete clearance of all lesions as determined visually and by palpation. BF-200 ALA was superior to both placebo (78.2 vs 17.1%; $p < 0.0001$) and MAL cream (78.2 vs 64.2%; $p < 0.05$) with respect to patient complete clearance rates. Almost all subjects reported adverse effects. These fell within the expected range of adverse effects experienced with previous formulations and included local skin reactions and discomfort. Overall, these effects were well tolerated [57].

In 2009, Hauschild *et al.* reported the findings of two placebo-controlled Phase III studies of 5-ALA patch (product code PD P506A). Current formulations require long incubation times [58]. In addition, scales and crusts need to be ablated before application and treated regions need to be protected from light after treatment. The self-adhesive patch can overcome these disadvantages because it can be applied directly to the lesions without the need for scraping and the patch itself is light-protective. The investigators compared 5-ALA patch with placebo patch and cryotherapy. After 12 weeks of treatment, 5-ALA patch was superior to placebo ($p < 0.001$) and cryosurgery ($p = 0.007$) with regard to complete clinical clearance rates. The most common adverse reaction reported was mild-to-moderate itching [58].

Celecoxib

A well-known NSAID, celecoxib acts by inhibiting the enzyme COX-2, thereby blocking prostaglandin synthesis. Evidence based on experimental data suggest that COX-2 may be involved in tumorigenesis in non-melanoma skin cancer. In 2010, Elmets *et al.* reported the results of a Phase II–III clinical trial to determine whether oral celecoxib can be used as chemoprevention of AK, BCCs and cutaneous SCC in high-risk individuals. Individuals were defined as high risk if they had a large number of AKs and were Fitzpatrick skin types I, II and III [59]. Participants took 200 mg of celecoxib or placebo twice-daily for 9 months. They were evaluated for efficacy and safety at 3, 6, 9 and 11 months after randomization. Although there was no significant difference between the celecoxib group and the placebo group with regards to the development of AK, there was a difference between groups in the development of BCC (response rate = 0.40; 95% CI: 0.18–0.93; $p = 0.032$) and SCC (response rate = 0.42; 95% CI: 0.19 to 0.93; $p = 0.032$). There was no difference between groups in the development of adverse effects. This study suggests that celexoxib may prevent non-melanoma skin cancer in patients who have AK and may be useful as chemoprevention, but long-term use needs to be studied further and balanced against the well-known side effects of NSAIDs [59].

Current treatments for BCC

Various modalities can be utilized for the treatment of BCC. Factors that are considered when determining the treatment strategy include overall health status, histologic tumor type, location, size and primary versus recurrent tumor [60]. Due to the low metastatic potential of BCC, treatment focuses on local control [61]. Treatment of BCC can be divided into surgical and nonsurgical categories. Surgical approaches include surgical excision (including Mohs surgery)

and cryotherapy. Nonsurgical approaches include radiotherapy (RT), imiquimod 5% cream, topical 5-Fu and PDT.

Surgical excision is a common method for treating BCC. Primary lesions of any size on the neck, trunk, arms or legs have a 5-year cure rate of more than 99% with surgical excision when completely excised [62]. However, recurrence of the tumor occurs in 21–41% of patients with incompletely excised lesions [63,64]. Mohs surgery is commonly used for patients who present with large (>2cm) tumors, high-risk morphea type BCC, recurrent tumors, or tumors located in cosmetically sensitive locations such as the face [6]. The lowest recurrence rates are obtained with Mohs surgery, with a 5-year recurrence rate of 1.0% for primary tumors and 5.6% for recurrent tumors [65].

Electrodessication and currettage (ED&C) is the most common method used by dermatologists to treat primary nodular and superficial BCC less than 1.5 cm in diameter [6]. Recurrence rates rise dramatically with increasing tumor size [66]. One study showed significantly higher recurrence rates for tumors in the mask area of the face and for tumors greater than or equal to 6 mm in diameter located on the cheek, forehead, scalp or neck [67]. Another disadvantage with ED&C is the potential risk of developing a scar. Overall, if selected appropriately, ED&C is an efficacious and cost-effective treatment modality [6].

Cryosurgery is commonly used to treat BCC, but is best reserved for tumors with well-defined borders. The 5-year recurrence rate is 4–17% [68]. Cryosurgery is also associated with adverse outcomes such as pain, tenderness, bulla formation, erythema, sloughing of necrotic tissue and localized edema [69].

RT is a nonsurgical option for patients with tumors in difficult-to-treat locations and for those who are not surgical candidates. Definitive RT is useful for treating early-stage skin cancers in locations where resection would result in a significant cosmetic and/or functional deficit [70]. RT has a cure rate of over 90% for most skin tumors [65]. The 5-year recurrence rates are 7.4% for primary BCC and 9.5% for recurrent BCC [62]. RT is not recommended in younger patients because new skin cancers may arise from RT field scars and long-term cosmetic results are poor [71]. Side effects include radionecrosis, atrophy and formation of telangiectasias [71].

Imiquimod 5% is used for AK as described previously and is also FDA approved to treat biopsy-proven, small (<2cm in diameter), primary, superficial BCC on the trunk, neck, arms or legs of adults with normal immune systems [61]. Imiquimod, applied once-daily five-times per week, has an 82% histologic clearance rate when used to treat BCC [72]. Since long-term clearance rates are not as high as other treatments, it is more commonly used as an adjunctive therapy or an alternative for patients who are not surgical candidates.

Topical 5-FU has been approved by the FDA to be applied twice-daily for at least 6 weeks in the treatment of BCC when traditional methods are not feasible. 5-FU is sometimes used to treat small, superficial BCCs and should only be used on low-risk sites [71]. It generally has low clearance rates compared with other modalities. One study demonstrated a 5-year recurrence rate of 21% when treated with a high concentration, 25% fluorouracil paste [73]. As when used to treat AK, 5-FU is associated with severe local side-effects including pain, burning, pruritus, irritation, inflammation, swelling, tenderness, hyperpigmentation and scarring [73].

PDT is used in the treatment of BCC, typically in cosmetically sensitive areas such as the face. One study of superficial and nodular BCC treated with PDT showed that 89% of lesions cleared with an overall cure rate of 79% after a mean follow-up of 35 months [74]. Side effects associated with PDT include localized effects such as stinging, burning, erythema and edema. Despite relatively good efficacy with PDT, it is a fairly inconvenient treatment option due to the necessity for multiple office visits and the adverse side effects.

Emerging treatments for BCC

■ Ingenol mebutate

Ramsay *et al.* conducted a Phase I/II clinical trial to examine the efficacy of *E. peplus* sap in treating non-melanoma skin cancer. A total of 36 patients with BCC, SCC and intra-epidermal carcinoma (IEC) were topically treated with 100–300 µl of sap, containing approximately 200 µg ml^{-1} of ingenol mebutate (Table 2) [44]. They were deemed to be nonsurgical candidates based on the nature or site of the tumor, age, use of anticoagulant drugs or because they had failed previous surgical or topical treatments. A total of 48 lesions were treated with daily treatments for 3 days. Complete clinical response (the absence of tumor on clinical exam) rates at 1 month post-treatment were 82% for BCC, 94% for IEC and 75% or SCC. Partial response was demonstrated in 18% of lesions and these lesions underwent another course of treatment 1 to 3 months later. Lesions were re-evaluated between 2 and 31 months later (mean = 15 months) and complete clinical response was seen in 57% of BCC, 75% of IEC and 50% for SCC [44].

Siller *et al.* conducted a randomized, vehicle-controlled, Phase IIa study evaluating 60 patients with superficial BCC treated with topical ingenol mebutate at 0.0025, 0.01 or 0.05% versus vehicle gel [75]. Two separate arms of the study were randomized – one receiving treatment on day 1 and 2 while the other was treated on day 1 and 8. Main outcome measures were adverse reactions. A secondary measure was clinical response at day 85. Erythema and scaling/dryness at the application site were the most common adverse reactions occurring at 75 and 50%, respectively. The incidences of skin reactions, such as edema, erosion and vesicles, were considered severe and were greatest in the 0.05% ingenol mebutate gel group. Ten severe reactions were seen in six patients, all of which resolved within a week and the remaining local skin reactions resolved prior to the conclusion of the study. Severe reactions were seen in the 0.05% gel group and the authors concluded that adverse reactions appeared to be dose-dependent [75]. In the ITT sample, 63% of the BCC lesions treated with 0.05% ingenol mebutate gel showed complete clinical response on days 1 and 2 ($p = 0.031$ vs vehicle) [75]. Histological clearance was observed in 71% of lesions in the as-treated group with 0.05% ingenol mebutate gel on days 1 and 2, whereas application of 0.05% gel on days 1 and 8 demonstrated complete clinical clearance in 13% and histological clearance of 38% [75]. These results suggest that ingenol mebutate may be a good alternative treatment of BCC due the convenience of only few treatments and its safety. Results of a similar study examining nodular BCC and ingenol mebutate have not yet been released (clinicaltrials.gov NCT00108121).

Table 2. Clinical trials of treatments for basal cell carcinoma completed between 2009 and 2012.

Treatment	Number of patients	Results	Most common adverse effects	Authors (Year)	Ref.
Ingenol mebutate – 100–300 µl of *Euphorbia peplus* sap, which contains 200 µg ml^{-1} of ingenol mebutate applied topically to AK daily for 3 days	36 (48 lesions [28 BCC])	Complete response: 82% for BCC 94% for IEC 75% for SCC	Desquamation, necrosis	Ramsay *et al.* (2011)	[44]
Ingenol mebutate – gel concentrations of 0.0025, 0.01 or 0.05% applied twice, either on days 1 and 2 or on days 1 and 8	60	65% response to 0.05% ingenol mebutate gel	Erythema, scaling, dryness	Siller *et al.* (2010)	[75]
Vismodegib – 150 mg orally	104	43% response rate in locally advanced BCC, 30% in metastatic BCC	Muscle spasms, alopecia, dysgeusia , weight loss, fatigue, nausea	Dirix *et al.* (2011)	[77]
LDE225 – 0.75% cream twice daily over 4 weeks vs vehicle cream	8 (27 lesions)	Three complete response, nine partial response, one no response	None reported	Skvara *et al.* (2011)	[78]

AK: Actinic keratoses; BCC: Basal cell carcinoma; IEC: Intra-epidermal carcinoma; SCC: Squamous cell carcinoma.

■ Vismodegib (GDC-0449)

As research continues to implicate the aberrant Hedgehog (Hh)-signaling pathway in the carcinogenesis of BCC as well as other neoplasias, new treatments are being developed that target this pathway. Vismodegib is small molecule that has been shown to inhibit the Hh-pathway and is being investigated as a treatment for various cancers [76].

In 2011, the findings of a Phase II trial of vismodegib for treatment of BCC were presented at the European Multidisciplinary Cancer Conference in Sweden [77]. During this trial, 150 mg daily oral dose was administered to 104 patients with advanced BCC until disease progressed or intolerable toxicity developed. The trial showed an overall response rate of 43% in locally advanced BCC and 30% in metastatic BCC. In diseases that progressed, an average of 9.5 months without progression was recorded. In 75% of patients taking vismodegib, tumors either regressed or were stabilized. Adverse effects included muscle spasms, hair loss, altered taste, weight loss, fatigue, nausea, decreased appetite and diarrhea. During the study, seven patients died; however, the investigators do not relate their fatalities to vismodegib treatment but rather to their pre-existing disease process [77]. It was approved in January 2012 by the FDA for locally advanced BCC as well as metastatic BCC that are not candidates for surgery or radiation.

■ LDE225

In recent double-blind, randomized,

vehicle-controlled, intra-individual study conducted by Skvara *et al.*, LDE225, a selective inhibitor of the *SMO* gene, was examined in the treatment of nevoid BCC syndrome [78]. The study evaluated the response in eight patients, with a total of 27 lesions. Patients were treated topically twice a day for 4 weeks with 0.75% LDE225 cream. Results showed clinical response, complete regression or a significant decrease in size of the lesion, in 12 of 13 of lesions treated with LDE225 [78]. The vehicle gel and the treatment were well tolerated with minimal systemic absorption. The apparent lack of local or systemic adverse effects with LDE225 is advantageous. None of the lesions, however, showed complete histological clearance of cancerous cells. Further studies would be need to be conducted to evaluate long-term efficacy, ideal treatment duration and potential long-term side effects of LDE225 cream [78].

Future perspective

In the USA, the prevalence of non-melanoma skin cancer and AK is likely to increase as the percentage of the aged population increases. Advances in the understanding of the molecular underpinnings of these diseases has lead to interest in novel drugs as alternatives to surgery and traditional medical treatments that are inconvenient and may have side effects that are difficult to tolerate.

Ingenol mebutate, which has been tested for AK, SCC and BCC, holds a great deal of promise because it requires only two to three doses, is safe, tolerable and efficacious. Trials that compare ingenol mebutate to diclofenac, 5-Fu and imiquimod would be very informative. However, it would be inherently difficult to truly blind such studies. When well-trained physicians administer the treatments, they may be biased by their familiarity with them. Ingenol mebutate is FDA-approved for the treatment of AK. More studies will need to be conducted to solidify this drug as an adequate alternative to current treatments for SCC and BCC.

The need for effective alternative treatments for BCC and SCC are paramount for patients with disease that are refractory to current treatment, or unable or unwilling to undergo surgery. One of the most promising avenues of research targets various aspects of the Hh-signaling pathway. Recent FDA approval of the Hh pathway inhibitor vismodegib for the treatment of BCC opens a new and exciting avenue for establishing pharmacological therapies. Over the next few years, it is anticipated that data from current studies will be published and further potential therapeutic options can be reassessed.

Dobesilate, 5-Fu/SA and cetuximab hold promise, but the number of studies is limited. More studies and trials with larger samples will further elucidate if these drugs will be good alternatives in the future.

Executive summary

Current treatments for actinic keratoses & squamous cell carcinoma

- Lesion-directed treatments include surgical excision, curettage, cryotherapy and lasers.
- Field-directed treatments include photodynamic therapy, imiquimod 5% cream, diclofenac 3% in hyaluronic acid (HA) gel, and topical 5-fluorouracil (5-Fu) in varying strengths.

Emerging treatments for actinic keratoses & squamous cell carcinoma

- Ingenol mebutate has been investigated for actinic keratoses (AK), squamous cell carcinoma (SCC) and basal cell carcinoma (BCC). Ingenol mebutate acts in two phases – an acute necrolytic phase and a delayed inflammatory phase. This is likely the reason it requires only two to three doses to be effective.
  - Three clinical trials of ingenol mebutate for AK were published in the past 3 years and all show superiority to vehicle gel in terms of clearance of lesions. It is US FDA-approved for the treatment of AK.
  - One trial was published that studied the sap of *Euphorbia peplus* as a topical treatment for SCC and BCC. The active ingredient is ingenol mebutate. Statistically significant increases in clearance rates, as compared with placebo, were found.
- Dobesilate is a synthetic molecule with antiangiogenic and antiproliferative properties that was investigated in one small trial for AK. Complete clearance was seen in 70% of patients and partial response was seen in 20% of patients.
  - 5-Fu/salicylic acid was compared with diclofenac HA and vehicle gel in one study for the treatment of AK. This study was unique because it assessed histologic clearance via biopsy. 5-Fu/SA was found to be statistically superior to both vehicle and diclofenac in terms of histologic clearance.
  - Cetuximab is an anti-EGFR monoclonal antibody that was tested in one study as a systemic treatment for advanced or inoperable SCC. It was found to cause disease regression or stabilization with a mean survival of 8.1 months.

Current treatments for BCC

- Surgical approaches include surgical excision (including Mohs surgery) and cryotherapy.
- Nonsurgical approaches include radiotherapy, imiquimod 5% cream, topical 5-Fu, and photodynamic therapy.

Emerging treatments for BCC

- Ingenol mebutate has been investigated as a treatment for BCC. Two such studies have been published since 2009 and they demonstrated response rates of 65 and 82%.
- Vismodegib is a small molecule that inhibits Hh-signaling that is a potential systemic therapy for BCC. There have been multiple clinical trials and the most recent one showed 43 and 30% response rates in locally advanced and metastatic BCC, respectively. It is FDA approved for locally advanced BCC as well as metastatic BCC, which are not candidates for surgery or radiation.
- LDE225 is a topical cream that selectively inhibits smoothened gene expression. It was recently studied in treating nevoid basal cell carcinoma syndrome. It showed significant clinical response over 4 weeks in 12 of 13 lesions with no local or systemic side effects.

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