New Therapeutic Options for Actinic Keratosis and Basal Cell Carcinoma

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Abstract
Actinic keratosis (AK) is a common premalignant skin lesion that is frequently treated by cryosurgery. Basal cell carcinoma is the most common malignancy of man, and early-stage lesions are usually cured via surgery. Advanced basal cell carcinoma may require more extensive surgery resulting in deformity, and many advanced lesions cannot be treated surgically. Several recent developments have improved therapeutic options for both conditions. Cryosurgery is still a mainstay of treatment for AK, but the introduction of effective topical agents, imiquimod cream and ingenol mebutate, has provided alternatives to cryosurgery. For advanced basal cell carcinoma, the small-molecule inhibitor vismodegib has proven to be an effective therapy for lesions that are not amenable to surgery and has demonstrated ability to achieve dramatic improvement in advanced, potentially disfiguring cancers.

Keywords
Actinic keratosis; basal cell carcinoma; imiquimod; ingenol mebutate; hedgehog pathway; vismodegib

Actinic Keratosis
Historically, cryosurgery has been the treatment of choice for AK and remains the most common approach to treatment. Nonsurgical options for AK include imiquimod and ingenol mebutate. Imiquimod received approval from the US Food and Drug Administration (FDA) in 1997 but has been formulated into more than one concentration or strength. Ingenol mebutate is a first-in-class therapy that could be joined by one or more ingenol products in clinical development. A 1927-nm fractional resurfacing laser has shown promise for AK in early clinical experience.

Imiquimod
Standard treatment with imiquimod has been 5% cream administered for 16 weeks for AK lesions involving 25 cm² of skin area. Recently, two additional concentrations received approval from the FDA: 2.5% and 3.75%. The less concentrated formulations offer advantages for patients who have difficulty tolerating the standard-strength formulation of the topical therapy.

In one trial,2 patients completed two 2-week treatment cycles, separated by a 2-week interval of no treatment. The second trial’s protocol included two 3-week treatment cycles with a 3-week nontreatment period in between.1 The primary end point of each trial was the proportion of patients who attained complete or partial response (>75% clearance) 8 weeks after completing treatment.

In the 3-week trial, the 8-week posttreatment assessment showed respective complete and partial response rates of 6.3% and 22.6% for the placebo group, 30.6% and 48.1% for imiquimod 2.5%, and 35.6% and 59.4% for imiquimod 3.75% (Figure 1). Both imiquimod groups had significantly higher response rates than did the placebo group (P<0.001). The 3.75% concentration led to a higher rate of partial clearance than did the 2.5% concentration (P=0.047).2

The median reduction in lesion count from baseline was 25% in the placebo group, 71.8% for imiquimod 2.5%, and 81.8% for imiquimod 3.75%. Both imiquimod groups had significantly greater reductions in lesion count than did the placebo group (P<0.001), and the 3.75% imiquimod concentration outperformed the 2.5% cream (P=0.048).2

In the 3-week trial, the 8-week posttreatment assessment showed respective complete and partial response rates of 5.5% and 12.8% for the placebo group, 25.0% and 42.7% for imiquimod 2.5%, and 34.0% and 53.7% for imiquimod 3.75% (Figure 2). Both imiquimod concentrations demonstrated superiority over placebo (P<0.001), and the 3.75% cream led to a significantly higher rate of partial response than did the 2.5% cream (P=0.034).1

The median reduction in lesion count was 23.6% with placebo, 66.7% with imiquimod 2.5% cream, and 80.0% with imiquimod 3.75% (P<0.001 for both imiquimod groups versus placebo).1

In both clinical trials, adverse events were considered manageable. Treatment discontinuation related to adverse events was uncommon. In the 2-week trial, temporary treatment interruption rates were 6.9% with imiquimod 2.5% and 10.6% for 1085-5629/13/$-see front matter © 2014 Frontline Medical Communications DOI: 10.12788/j.sder.0100

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imiquimod 3.75%.

Rates in the 3-week trial were 17.1% and 27.2% for the 2.5% and 3.75% imiquimod concentrations, respectively. Placebo-treated patients had no treatment interruptions in either trial.

Follow-up in both trials demonstrated durability of responses to imiquimod. In the 2-week trial, 33% of the imiquimod 2.5% group and 41% of the imiquimod 3.75% group had complete clearance of AK lesions. In the 3-week trial, complete clearance rates at 12 months were 43% with imiquimod 2.5% and 48% with imiquimod 3.75%.

**Ingenol Mebutate**

The precise mechanism of action for this agent remains unclear. The best available evidence suggests dual activity: mitochondrial depolarization within cells that make up AK lesions, followed by an internal inflammatory response that destroys the cells from the inside out. Ingenol mebutate has a rapid onset of action that allows for brief treatment intervals of 2 to 3 days depending on lesion location.

The FDA approved ingenol mebutate for AK in 2012. Other agents in the class are in various stages of clinical development. The treatment schema for ingenol mebutate varies by the skin area treated. For lesions on the face and scalp, standard treatment is 0.0015% ingenol mebutate gel, applied daily for 3 days. Patients who have lesions on the trunk and extremities are instructed to apply 0.05% ingenol mebutate gel for 2 days.

Patients treated with ingenol mebutate often have dramatic improvement in lesion status in a relatively brief period of time. In most cases, the agent reaches peak activity within the first week after the start of treatment. The activity manifests as an inflammatory reaction on the treated area, which intensifies for several days and then begins to resolve, usually within about a week.

Recently, the initial report of 12-month follow-up of patients treated with ingenol mebutate demonstrated the durability of responses. Among patients who had complete clearance of AK lesions following treatment, 87% maintained complete clearance 1 year later. The median time to recurrence of AK lesions on the face or scalp was 365 days.
Cryosurgery remains the most frequently used treatment for AK. However, results can vary, and the technique’s effectiveness is limited to visible lesions, leaving subclinical lesions untreated. Investigators in a phase III randomized, multicenter clinical trial evaluated sequential treatment of AK with cryosurgery followed by ingenol mebutate.\(^6\)

The trial included 329 patients, who were randomized to 0.0015% ingenol mebutate or vehicle, applied 3 weeks after cryosurgery. The primary objectives were the rates of complete clearance at 11 weeks and 12 months.\(^3\)

Recently reported 11-week results showed a significantly higher rate of complete clearance in patients treated with ingenol mebutate following cryosurgery (60.5% vs 49.4%, \(P=0.04\)). The combination therapy also was associated with a numerically greater reduction in the number of AK lesions than with cryosurgery alone (82.7% vs 75.6%).\(^5\)

The 11-week results are encouraging, but more important is the durability of results 1 or 2 years later. Combining multiple therapies with proven efficacy may offer the best strategy for attaining good long-term results.

**Laser**

Treatment with a 1927-nm fractional resurfacing laser has shown promise for AK in early clinical evaluations. A recently reported small clinical trial yielded encouraging results.\(^6\)

The study involved 24 adults with facial photodamage and AK. They underwent as many as four treatments with a fractionated 1927-nm nonablative thulium laser. One month after the final treatment, the total number of AK lesions had decreased by 91.3%. At 6 months, independent clinician assessment showed an 86.6% reduction from baseline in the number of lesions. Patients reported marked or noticeable overall improvement in photodamaged skin.\(^6\)

Investigators have yet to report long-term safety, tolerance, or efficacy data. Moreover, the mechanisms involved in AK clearance have not been determined. However, short-term clinical and histologic findings, combined with high patient-reported satisfaction and safety, suggest that the nonablative laser therapy has potential for treatment of AK.

**Basal Cell Carcinoma**

In 2012, the FDA approved vismodegib for locally advanced and metastatic basal cell carcinoma (BCC). Locally advanced BCC is a new diagnostic category, whose precise definition remains undetermined.

Diagnostic criteria for locally advanced BCC are not purely objective. Objective parameters include lesion size, extent of local invasiveness, location, expected morbidity and mortality from surgery or radiation therapy, low likelihood of curative resection, and contraindications to surgery (Figure 3).

Dermatologic specialists may apply subjective criteria to define locally advanced BCC, depending on their approach to treatment. A dermatologist who is inclined to treat a lesion surgically might define locally advanced by the extent of invasiveness, presence of perineural involvement, likelihood of curative resection, and the anticipated morbidity and mortality associated with the surgery. A dermatologist oriented toward medical treatment might apply criteria that are more relevant to a medical approach, such as requirement for therapy that goes beyond standard care to achieve definitive results (such as surgery).

Development of the science behind vismodegib began with the observation that BCC has a specific association with a loss-of-heterozygosity (LOH) polymorphism at chromosome 9q.\(^2\)

Additionally, Gorlin syndrome, which is characterized by development of multiple BCC lesions, tracks to LOH at 9q.

Patients with Gorlin syndrome have a predisposition to other neoplasms, including medulloblastoma, meningioma, jaw cysts, skin lesions, and mesentery fibromas of the heart and ovaries. Affected patients also have developmental abnormalities involving ribs, craniofacial structures, and mental function, as well as polydactyly, syndactyly, and spina bifida.

Subsequent genetic investigations revealed mutations in **PTCH1** (usually loss-of-function mutations) associated with both Gorlin syndrome and sporadic BCC.\(^8-10\) Other studies identified mutations in the Smoothened (**SMO**) gene in sporadic BCC. Mutations in **PTCH1** and **SMO** lead to aberrant signaling in the Hedgehog pathway.

In the normal state, Hedgehog signaling is involved in regulating embryonic development, including appropriate growth, location, and cellular content tissues and organs. Hedgehog signaling has limited activity in adult tissues. However, reactivation of Hedgehog signaling has been associated with tumorigenesis.\(^11\)

Abnormal Hedgehog signaling in BCC is often the result of loss-of-function mutations in **PTCH1**. Mutated **PTCH1** releases its normal inhibition of **SMO**, leading to aberrant activation of the transcriptional factor **Gli** in the cytoplasm. Once activated, **Gli** enters the cell nucleus to activate multiple genes involved in proliferation and cell-cycle regulation, including **Wnt, TGF-B, PTCH1**, and **Myc**. Oncogenic activation blocks normal programmed cell death (apoptosis), resulting in unregulated cell growth and proliferation.
The Hedgehog inhibitor vismodegib restores normal signaling by binding SMO protein and inhibiting Gli activation. A series of published reports have documented vismodegib’s activity in patients’ BCC lesions, often resulting in dramatic improvement in disfiguring lesions (Figure 4).

Although not currently approved for Gorlin syndrome, vismodegib has continued the clinical success seen in locally advanced and metastatic BCC. In many instances, single-agent vismodegib has led to complete or near-complete clearance of severe and numerous lesions in patients with Gorlin syndrome.12,13

In general, vismodegib has been tolerated with few grade 3/4 adverse events reported.14 The most frequently reported adverse events have been muscle spasms, dysgeusia, alopecia, diarrhea, nausea, fatigue, and weight loss.

Most recently, the antifungal agent itraconazole has been evaluated as potential therapy for BCC. A phase II open-label study involving 19 patients with BCC showed that treatment with itraconazole had a modest impact on tumor area (a reduction of 24% from baseline).15 The modest lesion improvement was associated with a 45% reduction in BCC proliferative activity (as determined by assessment of the proliferation marker Ki-67) and a 65% reduction in Gli activation.

Clinical experience with vismodegib in BCC has raised almost as many questions as it has answered. The minimum duration of therapy has yet to be determined, which, in turn, affects the choice and definition of the therapeutic end point. Although systemic therapy with vismodegib has proven effective, a topical formulation would be welcomed. As is true of most novel agents, the drug is expensive, which could help increase the appeal of generic itraconazole (or another older drug) if its efficacy were comparable.

Reported resistance to vismodegib has been limited, unlike with the use of targeted therapies for melanoma, but clinical experience with the Hedgehog inhibitor is more limited. Data on long-term outcomes have not become available, although studies are under way. Biomarkers that correlate with response to vismodegib have not been identified.

The answers to these and other questions about vismodegib’s safety and efficacy will likely influence the agent’s future in the treatment of BCC.

Summary

Advances in the treatment of AK have occurred that empower the clinician with greater treatment options. Newer lower-strength formulations of imiquimod cream have promise for improving tolerability without risking efficacy. Accumulating experience with ingenol mebutate suggests that the therapeutic effects are durable. Evaluation of ingenol mebutate as an adjunct to cryotherapy has shown promise for improving on results that can be obtained with cryotherapy alone. The development of vismodegib has been a major advance in the treatment of advanced BCC. Optimizing use of the therapy awaits resolution of issues related to duration of therapy, identification of biomarkers that correlate with treatment success (or failure), the potential for developing a topical formulation of the drug, and assessment of long-term data on safety and efficacy.

**Figure 4.** Activity of Oral Vismodegib in Locally Invasive Basal Cell Carcinoma. Vismodegib, a central mediator of Hedgehog pathway signaling, was used in a trial of patients with locally invasive BCC. The photos show a 60-year-old man with basal cell nevus syndrome on the posterior scalp at baseline (A) and after 5 months of therapy (B); and a 41-year-old woman with facial lesions at baseline (C) and after 2 months of treatment (D).

References


