Dilemmas and Challenges in Skin Cancer Therapies and Management

Field vs. Lesional Therapies for AKs

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The University of Iowa
DISCLOSURE OF RELEVANT RELATIONSHIPS WITH INDUSTRY

Field vs. Lesional Therapies for AKs
S021 – Dilemmas and Challenges in Skin Cancer Therapies and Management
2/17/2018, 9:00 AM
Room 5A
Roger I. Ceilley, M.D.
BioFrontera - Consultant
Leo Pharmaceuticals - Consultant
Sun Pharma – Consultant

THERE WILL BE OFF LABEL DISCUSSIONS
Treatment of AK: Aim

- Prevention of SCC invasion and metastasis
- Provide long-term disease control
- Relief of symptoms
- Improvement of cosmetic appearance
- Proactively treat subclinical lesions
Disease Continuum of AK to Invasive SCC
### Disease Continuum of AK to Invasive SCC:

#### Invasive SCC

<table>
<thead>
<tr>
<th>Number of AKs</th>
<th>Relative patient risk for SCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 or fewer</td>
<td>1.0</td>
</tr>
<tr>
<td>6 - 20</td>
<td>4.0</td>
</tr>
<tr>
<td>&gt; 20</td>
<td>20.0</td>
</tr>
</tbody>
</table>

Pain as a Marker of AK or SCC

Spontaneous Pain
- AK = 15%
- SCC = 57.5%

Pain with Pressure
- AK = 25%
- SCC = 80%
Field Cancerization: Histology vs Optical Coherence Tomography vs Confocal

Markovitz et al. Poster, Fall Clinical Derm Symp. Las Vegas NV, October 2014
Actinic Keratosis

Gene Expression Patterns of Normal Human Skin, Actinic Keratosis, and Squamous Cell Carcinoma

A Spectrum of Disease Progression

R. Steven Padilla, MD, MBA; Sheldon Sebastian, MD; Zeyu Jiang, PhD; Ingo Nindl, PhD; Richard Larson, MD, PhD

Objectives: To identify and compare the gene expression profiles of actinic keratosis (AK) and squamous cell carcinoma (SCC) and to further clarify critical genetic alterations in the evolution of SCC from normal sun-damaged human skin.

Design: Observational study.

Setting: University practice.

Patients: Skin biopsy specimens were obtained from 16 patients. The specimens included 14 normal non-sun-exposed skin samples, 14 normal sun-exposed skin samples, 5 AKs, and 15 cutaneous SCCs.

Main Outcome Measures: Gene expression profiles from normal non-sun-exposed skin, normal sun-exposed skin, AKs, and SCCs.

Results: Using a highly astringent shrunken centroid threshold of 6.52 and the prediction analysis of microarrays, we identified 89 unique genes that most likely contribute to the molecular evolution of SCC. Our model was cross-validated using data from a separate study and clearly distinguishes between skin tumors (AK and SCC) and normal skin independent of sun exposure. Genes that were upregulated in AK and SCC were downregulated in normal skin, and genes that were downregulated in AK and SCC were upregulated in normal skin.

Conclusions: The finding of similar differentially expressed genes in AK and SCC confirms that AK is a precursor lesion of SCC and indicates that they are closely related genetically. Clear elucidation of these relationships will be critical to improving therapeutic approaches.

Arch Dermatol. 2010;146(3):288-293
Actinic Keratosis

Direct correlation of abnormal gene expression in the progression of Normal skin to Sun exposed to AK to SCC

- AK and SCC - most evident degree of gene expression

Evaluation of the Prognostic Significance of Follicular Extension in Actinic Keratoses

SHAILLY PANDEY, BA; STEPHEN E. MERCER, MD, PhD; KAI DALLAS, BS; PATRICK O. EMANUEL, MD; GARY GOLDENBERG, MD

Mount Sinai School of Medicine, New York, New York; Departments of Dermatology and Pathology, Mount Sinai School of Medicine, New York, New York; Consultant Dermatopathologist Diagnostic Medlab, Auckland, New Zealand
Prognostic significance of follicular extension in Actinic Keratosis

## Table 1: Cancer occurrences versus history of actinic keratosis with follicular extension.

<table>
<thead>
<tr>
<th></th>
<th>Squamous cell carcinoma</th>
<th>Basal cell carcinoma</th>
<th>Melanoma</th>
<th>No cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>With follicular extension</td>
<td>64 (52%)</td>
<td>40 (54%)</td>
<td>11 (61%)</td>
<td>30 (41%)</td>
</tr>
<tr>
<td>Without follicular extension</td>
<td>60 (48%)</td>
<td>34 (46%)</td>
<td>7 (39%)</td>
<td>44 (59%)</td>
</tr>
<tr>
<td>Total</td>
<td>124</td>
<td>74</td>
<td>18</td>
<td>74</td>
</tr>
</tbody>
</table>
Actinic Keratosis - Follicular Extension
Increased risk factor for skin cancer especially Melanoma

Table 2: Univariate odds ratio comparing previous history of skin cancer in patients with AKs without follicular extension to patients with AKs with follicular extension.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Odds ratio</th>
<th>Confidence interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell carcinoma</td>
<td>1.18</td>
<td>0.67-2.04</td>
<td>0.57</td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td>1.30</td>
<td>0.72 - 2.27</td>
<td>0.38</td>
</tr>
<tr>
<td>Melanoma</td>
<td>11.1</td>
<td>1.56-111</td>
<td>0.04</td>
</tr>
<tr>
<td>Overall</td>
<td>1.81</td>
<td>1.01-3.22</td>
<td>0.043</td>
</tr>
</tbody>
</table>

Strong recommendation for field therapy and closer surveillance

Actinic keratosis as a marker of field cancerization in excision specimens of cutaneous malignancies

n=149 excision specimens BCC, SCC & MM

Table 1: Incidence rates of AK by cutaneous malignancy

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th># of Cases Examined (% of Total Cases)</th>
<th># of Cases with AKs Observed (% by Cancer Type)</th>
<th># of Cases with Marginal AKs (% of Previous Column Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCC</td>
<td>64 (43%)</td>
<td>21 (33%)</td>
<td>13 (62%)</td>
</tr>
<tr>
<td>SCC</td>
<td>61 (41%)</td>
<td>35 (57%)</td>
<td>20 (57%)</td>
</tr>
<tr>
<td>MM</td>
<td>24 (16%)</td>
<td>6 (33%)</td>
<td>2 (33%)</td>
</tr>
<tr>
<td>Total</td>
<td>149 (100%)</td>
<td>62 (42%)</td>
<td>35 (56%)</td>
</tr>
</tbody>
</table>

Actinic keratosis as a marker of field cancerization in excision specimens of cutaneous malignancies

Strong recommendation for field therapy and closer surveillance

Ask your Dermatopathologist to comment on AK follicular invasion and AKs associated with other skin cancers on biopsy / excision reports.
Risk of Progression of AK to KC

<table>
<thead>
<tr>
<th>Time</th>
<th>AK to SCC</th>
<th>AK to Invasive SCC</th>
<th>AK to BCC</th>
<th>AK to KC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>0.60%</td>
<td>0.39%</td>
<td>0.48%</td>
<td>0.48%</td>
</tr>
<tr>
<td>2 years</td>
<td>1.46%</td>
<td>1.06%</td>
<td>1.04%</td>
<td>1.04%</td>
</tr>
<tr>
<td>3 years</td>
<td>2.25%</td>
<td>1.79%</td>
<td>1.26%</td>
<td>1.26%</td>
</tr>
<tr>
<td>4 years</td>
<td>2.57%</td>
<td>1.97%</td>
<td>1.56%</td>
<td>1.56%</td>
</tr>
<tr>
<td>5 years</td>
<td>3.39%</td>
<td>2.50%</td>
<td>2.27%</td>
<td>2.27%</td>
</tr>
</tbody>
</table>

Risk was calculated using the Kaplan-Meier method.
Conclusions

➢ The study quantified the risk of progression of AKs on the face and ears to SCC in a high-risk population

➢ Demonstrates transformation of AKs to BCC

➢ Verifies untreated AKs have a high rate of clinical regression

➢ AKs may play a greater role in the overall burden of keratinocyte carcinomas than previously documented

➢ Suggests approximately two-thirds of SCCs and one-third of BCCs initially present as AKs

Chronic condition “Actinic Neoplasia Syndrome”
Currently available agents are effective. Choosing a treatment regimen depends on:

- Severity / extent of clinical presentation
- Downtime and tolerability
- Cost
Available Treatments for AK’s

- **Cryosurgery**
- **Surgery**
  - Curettage and electrodessication
  - Excision
  - Laser ablation
  - Chemical peeling
- **Topical Agents**
  - 5-FU
  - Diclofenac
  - Imiquimod
  - Ingenol mebutate
- **Photodynamic therapy**
AK Treatment Modalities Efficacy

% Complete Clearance

- 5% 5-FU: 43%
- 0.5% 5-FU: 52%
- 4%: 54%
- Diclofenac: 50%
- Imiquimod: 45-50%
- Ingenol Mebutate: 40-50%
- PDT: 55-73%
- New nanoemulsion ala pdt: 61-91%
Efficacy of Cryosurgery

- 2004 open study – 421 AK’s in 89 patients
- Variable freezing times
- Cure rates
  - 39% <5 seconds
  - 69% 5 – 20 seconds
  - 83% >20 seconds

A Prospective Study of the Use of Cryosurgery for the Treatment of Actinic Keratosis

Figure 2 Percentage of complete response lesions with hypopigmentation as a function of the duration of freezing

Do You Know WHICH AK Will Progress to Invasive SCC?

Should all Actinic Keratoses be Treated?
AK

Subclinical actinic keratoses

Defective antigen presentation
HPV infection
Gene mutations

Excessive activation of suppressor cells
Damage to dendritic cells
Stimulation of Ras oncogene

Actinic Keratoses: The tip of the iceberg
AK Therapy: Topical 5-FU
most popular \textit{topical} AK Rx
GRAMPA!!
I EXCEEDED EXPECTATIONS!

D−
Nobody likes the side effects !!
Efficacy, Safety, and Tolerability of 4% 5-Fluorouracil Cream in a Novel Patented Aqueous Cream Containing Peanut Oil Once Daily Compared With 5% 5-Fluorouracil Cream Twice Daily

- Decreased adverse events vs traditional treatment
- Comparable results with 4 wk treatment
- The peanut oil component is safe in peanut-allergic patients

J Drugs Dermatol Oct 2016, Magdalene A. Dohil MD
AK Therapy: 5-FU

• Protocols to increase tolerance:
  – Intermittent / Pulse dosing
  – Concurrent use of corticosteroids
  – Subsequent use of corticosteroids
  – Limited areas treated sequentially
  – Stepped approach

*All decrease efficacy
Calcipotrine combined with 5-FU more effective

- Together BID x 4 days resulted in 87.8% reduction in lesions vs 20% for 5-FU alone.

- Optimally activates CD4+T cell-mediated immunity.

Cunningham et al, J Clinical Invest 2017;127(1)
CONCLUSIONS AND RELEVANCE:

A conventional course of fluorouracil to the face and ears substantially reduces surgery for squamous cell carcinoma for 1 year without significantly affecting the corresponding risk for basal cell carcinoma
5-Fluorouracil (My Preference)

- One day regimen (all strengths)
- Number of applications most important
- 21 days face
- 30-45 days for arms, trunk, scalp
- Add antihistamines, NSAIDs
- Topical steroids *after* treatment prn
- Use as pre-treatment for PDT and post treatment after cryo
5% Imiquimod treatment: Clinical Therapeutic Endpoint

Before

3 doses

2 weeks since last treatment
Complete Clearance Rates by Most Intense Erythema During the Study

% Complete Clearers

Test for Trend:  p<0.0001

Note: There were no subjects with complete response who had no erythema in the Imiquimod 3x/Week group.
Clinical Therapeutic Endpoint

- Clues exist that when AK becomes edematous, erythematous, eroded and crusted, it is probably doomed to die.

- Continuing Imiquimod does not improve efficacy, but will lead to more local reactions.
Imiquimod:

- Inflammatory response correlates with frequency of application
- Duration required to achieve clearance is variable
- Dependent variables: skin type, number of AKs, location and background sun damage
- Begin 1 – 3 times / week (unpredictable)
Sustained Field Clearance Rates in All Patients

Twelve months after end of treatment

Out of all treated patients (including in the denominator also those not cleared at end of therapy)

Imiquimod 3.75% Cream after Cryotherapy in the treatment of Hypertropic Actinic Keratoses on the Dorsal Hands and Forearms

Begin on the same day as cryotherapy

**Incidence of Hypertrophic AKs on the Dorsal Hands and Forearms**

<table>
<thead>
<tr>
<th>Visit</th>
<th>Baseline</th>
<th>Week 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Lesions</td>
<td>6.3</td>
<td>5.5</td>
</tr>
<tr>
<td></td>
<td>2.94</td>
<td>1.235</td>
</tr>
</tbody>
</table>

*P-value = 0.0064. P-values were for the comparison, by way of ANOVA with factors of patient and treatment, of mean change from baseline at each week post baseline for the cryotherapy + Imiquimod group compared to the corresponding week in the cryotherapy only group.*

Adherence
Ingenol Mebutate gel for Actinic Keratosis.

Face and Scalp 0.015% qd x 3

Trunk and Extremities 0.05% qd x 2

Efficacy of Ingenol Mebutate 0.05% Gel when used after Cryotherapy in the Treatment of Hypertrophic Actinic Keratoses (AK) on Dorsal Hands.

- Increased efficacy
- No significant increase in side effects when applied the same day

My Tips:

- 0.015% Chest; .05% Scalp
- Careful pre-treatment instructions
- Don’t forget cold storage
- Be Careful around the eyes
- Valcyclovir if hx of HSV or no prior H Zoster vaccination
- Cool compresses post treatment prn
- Topical steroids prn
- Ideal for use after Cryo for HT AKS on hands or scalp
Photodynamic Therapy: New Developments

- 10% ALA nano-emulsion with red light
- Short incubation of ALA PDT
- Sequential treatment with other modalities
- Treatment of extremities and actinic cheilitis
- Utilization of heat to improve efficacy
- Pain reduction techniques
- Treatment for field cancerization
- Daylight PDT
Complete Patient Clearance – per US PI Data for PDT Drugs

Future Treatment Trends?

Combination therapy
– Lesion-directed + field-directed
– Two field-directed agents
– Sequential or concurrent

Timed Sequential Therapy
CONCLUSIONS:

While rarely being imminently life-threatening, NMSC and AK have an impact on QL as quantified by the EQ-5D-5L. This impact is associated with diagnosis (AK vs. NMSC) and clinical progression (AK vs. AK plus SCC). Both lead to a clear decline in QL. This shows that disease progression is perceived and judged as detrimental by patients and that AK and NMSC should be diligently treated to preserve and restore QL.
Take Away Points

➢ Tailor treatment to the patients medical conditions, schedule, financial and insurance coverage and ability to tolerate side effects.

➢ New drugs and new formulations offer more treatment options.

➢ Try different approaches to see what works best for your patient.

➢ Sequential therapy appears to improve clearance rates, duration of clearance and clearance of hypertrophic AKs.
Field vs Lesional Therapies for AKs
When to use Which?

Lesional therapy for:
- Small number of lesions
- Painful lesions
- Hypertrophic lesions
- Hypertrophic lesions before field therapy
Field Therapy for AK:

- After destructive therapy
- Multiple non-hyperkeratotic lesions
- Large field involvement and Photodamage
- Field cancerization
- When there is evidence of follicular invasion on biopsy
- When found in association with cutaneous malignancies
- High risk patients. Ideal prior to immunosuppression