Dilemmas and Challenges in Skin Cancer Therapies and Management

Field vs Lesional Therapies for AKs
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DISCLOSURE OF RELEVANT RELATIONSHIPS WITH INDUSTRY

Field vs Lesional Therapies for AKs
S021 – Dilemmas and Challenges in Skin Cancer Therapies and Management

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: 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%

G Ital Dermatol 2016, Apr
Actinic Keratosis - Follicular Extension

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></th>
<th>Odds ratio</th>
<th>Confidence interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell</td>
<td>1.18</td>
<td>0.67-2.04</td>
<td>0.57</td>
</tr>
<tr>
<td>carcinoma</td>
<td></td>
<td></td>
<td></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

Background: Depth of follicular extension in AK correlates with depth of invasive SCC

- Histological review of 193 iSCC cases from Badalona, Spain
  - 63% classified as having originated from the “differentiated pathway”, 37% from “classical”
  - 25.9% (50/193) displayed follicular extension of atypical keratinocytes in an AK

“These results may provide an explanation for recurrence and for progression of some AKs following superficial destructive treatment modalities, such as cryotherapy, which are unlikely to reach the deeper levels of the follicular epithelium.”

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

n=149 excision specimens BCC, SCC & MM

<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 Keratoses: Natural History and Risk of Malignant Transformation in the Veterans Affairs Topical Tretinoin Chemoprevention Trial

Risk of Progression of AK to KC

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

- **Cryosurgery**
- **Surgery**
  - Curettage and electrodessication
  - Excision
  - Laser ablation
  - Chemical peeling

- **Topical Agents**
  - 5-FU
  - Diclofenac
  - Imiquimod
  - Ingenol mebutate

- **Photodynamic therapy**
## AK Field Treatment Modalities Efficacy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>5% 5-FU</td>
<td>43%</td>
</tr>
<tr>
<td>0.5% 5-FU</td>
<td>52%</td>
</tr>
<tr>
<td>4%</td>
<td>54%</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>50%</td>
</tr>
<tr>
<td>Imiquimod</td>
<td>45-50%</td>
</tr>
<tr>
<td>Ingenol Mebutate</td>
<td>40-50%</td>
</tr>
<tr>
<td>PDT</td>
<td>55-73%</td>
</tr>
<tr>
<td>New nano-emulsion ala pdt</td>
<td>61-91%</td>
</tr>
</tbody>
</table>

* Not head-to-head comparisons
Efficacy of Cryosurgery

- 2004 open study – 421 AK’s in 89 patients²
  - Variable freezing times
  - Cure rates
    - 39% <5 seconds
    - 69% 5 – 20 seconds
    - 83% >20 seconds

Damage to p53 gene
Stimulation of Ras oncogene
Gene mutations
Damage to p53 gene
Stimulation of Ras oncogene
HPV infection
Damage to dendritic cells
Defective antigen presentation
Excessive activation of suppressor cells

Subclinical actinic keratoses

Actinic Keratoses: The tip of the iceberg

Cryotherapy
ED
Laser
Field Therapy
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*
Calcipotriene 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)
Chemoprevention of Basal and Squamous Cell Carcinoma With a Single Course of 5-FU Cream

- JAMA Dermatol 2018 Jan 03;[EPub Ahead of Print]
- CONCLUSIONS AND RELEVANCE:
  A conventional course of fluorouracil to the face and ears substantially reduces surgery for squamous cell carcinoma for one year without significantly affecting the corresponding risk for basal cell carcinoma
5-Fluorouracil (My Preference)

- Once daily 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
Complete Clearance Rates by Most Intense Erythema During the Study

Test for Trend:  $p<0.0001$

Note: There were no subjects with complete response who had no erythema in the Imiquimod 3x/Week group.
Complete Clearance Rates by Erythema Intensity

Patients with complete clearance, %

- None: 16.7% (n = 6)
- Mild: 24.6% (n = 57)
- Moderate: 43.0% (n = 114)
- Severe: 86.8% (n = 38)

$P_{\text{trend}} < .0001$
Sustained Field Clearance Rates in All Patients

Twelve months after end of treatment

![Bar chart showing clearance rates for Imiquimod (73%), 5-FU (33%), and Cryotherapy (4%) for all patients. Imiquimod: t.i.w x 4 w. x 1-2 courses; 5-FU: b.i.d x 4 wks; Cryotherapy: 20-40 sec per lesion x 1-2 sessions.]

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 Hypertrophic Actinic Keratoses on the Dorsal Hands and Forearms

Begin on the same day as cryotherapy

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryotherapy + Imiquimod</td>
<td>6.3</td>
<td>3.236</td>
</tr>
<tr>
<td>Cryotherapy Only</td>
<td>5.5</td>
<td>2.94</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.

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 for Ingenol Mebutate:

- 0.015% Chest; .05% Scalp
- Careful pre-treatment instructions
- Don’t forget cold storage
- Be Careful around the eyes
- Valacyclovir 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

Vegter & Tolley EU naive analysis

Future Treatment Trends?

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

Timed Sequential Therapy
Take Away Points

- Tailor treatment to the patient’s medical conditions, schedule, financial and insurance coverage and ability to tolerate side effects.
- New drugs and new formulations offer more treatment options.
- Sequential therapy appears to improve clearance rates, duration of clearance and the clearance of hypertrophic AKs.
Lesional Therapies for AK

Lesional therapy for:
- Small number of lesions
- Painful lesions
- Hypertrophic lesions
- Hypertrophic lesions before or after 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