The Latest on AKs and Skin Cancer Prevention: New Supplements, Magical Lights, and Chemoprevention all in one day

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Dr. Bhatia’s Disclosures:

- Affiliations with Abbvie, Actavis, Allergan, Aqua, Bayer, Biofrontera, BiopharmX, Castle, Cipher, Dermira, Encore, Exeltis, Ferndale, Foamix, Galderma, Intraderm, ISDIN, LaRoche-Posay, Leo, Novan, Novartis, PharmaDerm, Pfizer, Promius, Regeneron, Sanofi, SunPharma, and Valeant

- Some slides from industry were borrowed for explanation of data and scientific background, not for promotion

- Off-label discussion is likely

- Copies of pdf or questions: bhatiaharbor@gmail.com
Objectives

- Review of Definitions
- Topical Prevention Strategies
- Systemic Approaches
- Photodynamic Therapy for Skin CA prevention
- Conclusions
First some definitions...

- What is the disease?
  - Actinic Keratosis can either regress, persists, or progress to SCC?
  - AK as a symptom of Photodamage, a disease that cannot be cured?
  - SCC *in situ* that should be treated to avoid recurrence or invasion?

Consider the sources

- “AK is the initial clinical manifestation of a disease continuum that progresses to frank SCC…”

- “Actinic Keratosis is a premalignant condition of thick, scaly, or crusted patches of skin.”
  - Referenced the textbook quotes from Bolognia and Fitzpatrick chapters and a Canadian FP article as seen in Wikipedia

*How we define this to patients and ourselves will help define expectations...*
Survey says...patients don’t care unless we make them care

- 571 pts surveyed at PSU-Hershey: 3 questions about AKs between June 1-July 31 2016, mean age 42, gender equal
- The question that presented AK as a “precancer” had the highest proportion (92.2%) responding they preferred treatment.
- Two questions presenting the risk of AK as not progressing to cancer yielded the lowest proportion of individuals who chose treatment [57.7%] and [60.9%].

Conclusions: pts’ decisions on whether to receive treatment for AK is significantly affected by physician wording, especially if made aware of risk of CA

Are Actinic Keratoses the cutaneous version of “cavities”?

- **Treatment**
  - Derms examine for AKs the same way dentists search for dental caries
  - One cavity today → ten cavities later
  - Filling cavities is like freezing AKs: *it is a bandage not a remedy*

- **Prevention**
  - *When you brushed your teeth, did you brush only one tooth or all of them?*
  - *Do we take that same approach for AKs?*
  - *Is sunscreen the same as toothpaste for the skin?*
What is a “Subclinical AK?”

- Evolving AKs are still AKs, whether we see them with our eyes, dermatoscope, confocal microscopy, or fluorescence.
- To reduce the risk of skin cancer, we treat what is coming and not just what we see today.

Malvehy, J., “A new vision of actinic keratosis beyond visible clinical lesions,” JEADV, 2015, 29 (supp) 1:3-8
Facts and Quotes

“Squamous cell carcinoma is the major cause of non-melanoma skin cancer related death”
- Weinstock, M. Arch Dermatol 129:1286-90, 1993

“cSCC is the 4th most common cause of death in renal transplant patients”
- Marcen, R. Transplant Proceedings

“Almost 50% of Caucasian Australians will develop a BCC before the age of 70…it is likely that the same person will develop another within three years.”
- Shumack, S. Aust Prescr 2011;34:6-731 Jan 2011
Deaths from Skin Cancer

- 52.5% Melanoma
- 47.5% CSCC

NCI-SEER program
Cancer Facts and Figures
Karla PS, Han J, Schmults CD
Do AKs grow up to become SCC?

- Anywhere between 0.025 and 16% of AKs can progress to invasive SCC
  - Extrapolation studies suggesting the risk of progression at approximately 8%
  - Risks vary with age, gender, chronic UV exposure, and location of AKs

- Spontaneous regression of AK
  - Estimated 15–25% in 1-year period

- Occurrence rate of invasive SCC
  - 5–20% over follow-up periods of 10–25 years
  - 0.1% and 0.24% transformation rate from AK to SCC in 1 year

- 82.4–100% pts with invasive SCC arising on sun-exposed areas have a history of AK


Broad variation in transplant patients developing SCC from AKs

### Table I. Adjusted odds ratios with 95% confidence intervals for risk of squamous cell carcinoma in relation to incidence, regression, and overall change in actinic keratoses counts

<table>
<thead>
<tr>
<th>Category of AK change</th>
<th>Overall, n (%)</th>
<th>Without SCC, n (%)</th>
<th>With SCC, n (%)</th>
<th>Adjusted OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total no. of incident AKs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3</td>
<td>93 (39)</td>
<td>89 (48)</td>
<td>4 (7)</td>
<td>Ref (P &lt; .05)</td>
</tr>
<tr>
<td>3–&lt;10</td>
<td>65 (27)</td>
<td>54 (29)</td>
<td>11 (20)</td>
<td>3.46 (0.66-18.16)</td>
</tr>
<tr>
<td>10–&lt;20</td>
<td>34 (14)</td>
<td>25 (14)</td>
<td>9 (17)</td>
<td>3.31 (0.54-20.18)</td>
</tr>
<tr>
<td>≥20</td>
<td>47 (20)</td>
<td>17 (9)</td>
<td>30 (56)</td>
<td><strong>9.52 (1.60-56.70)</strong></td>
</tr>
<tr>
<td><strong>Total no. of regressed AKs†</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3</td>
<td>62 (31)</td>
<td>59 (40)</td>
<td>3 (6)</td>
<td>Ref (P &gt; .05)</td>
</tr>
<tr>
<td>3–&lt;10</td>
<td>62 (31)</td>
<td>48 (33)</td>
<td>14 (26)</td>
<td>1.69 (0.28-10.35)</td>
</tr>
<tr>
<td>10–&lt;20</td>
<td>33 (17)</td>
<td>23 (16)</td>
<td>10 (19)</td>
<td>1.28 (0.16-10.04)</td>
</tr>
<tr>
<td>≥20</td>
<td>42 (21)</td>
<td>16 (11)</td>
<td>26 (49)</td>
<td>1.66 (0.14-20.40)</td>
</tr>
<tr>
<td><strong>Overall change in AK counts</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥10–≤+10</td>
<td>174 (73)</td>
<td>153 (83)</td>
<td>21 (39)</td>
<td>Ref (P &lt; .05)</td>
</tr>
<tr>
<td>&lt;10</td>
<td>35 (15)</td>
<td>20 (11)</td>
<td>15 (28)</td>
<td>0.44 (0.14-1.43)</td>
</tr>
<tr>
<td>&gt;+10</td>
<td>30 (13)</td>
<td>12 (7)</td>
<td>18 (33)</td>
<td><strong>3.77 (1.30-10.94)</strong></td>
</tr>
</tbody>
</table>

Bold indicates results reaching statistical significance.

AK, Actinic keratoses; CI, confidence interval; OR, odds ratio; SCC, squamous cell carcinoma.

*Adjusted for age, sex, skin cancer history, and baseline number of AKs.
†Participants with 0 AKs at baseline excluded.

Hot off the Press: Seborrheic keratosis (SK) may mimic cancer

- Dermatopathology samples from 2015:
  - “SK” or “ISK” “SK rule out others,” changing, growing, and so on—were excluded. A total of 4,361 eligible cases were identified and used for analysis.

- Of total cases identified as only “SK” or “ISK” in the clinical data, 3,759 (86.2%) were, in fact, SK or ISK.

- A total of 466 (10.7%) were an assortment of non-malignancy diagnoses, such as dermatofibroma.

- There were 136 (3.1%) cases histologically diagnosed as malignancies.

- The majority (9/136 cases; 67%) were in situ or invasive squamous cell carcinoma; 24.3% (33/136) were basal cell carcinoma and 8.8% (12/136) were melanoma.

Chen TY, Morrison AO, Cockerell CJ, “Cutaneous malignancies simulating seborrheic keratoses: An underappreciated phenomenon?” J Cutan Pathol. [Published online ahead of print July 2, 2017].
Hot off the Press: Vitamin D Receptor Polymorphism Increasing NMSC risks?

- Protection from cumulative UV that induces NMSC is exerted via signaling mechanisms involving the vitamin D receptor (VDR)
  - Single-nucleotide polymorphisms in VDR can potentially increase NMSC risk: 3 mutations types ApaI, BsmI, and TaqI

- Study evaluating 200 patients, matched for high risk factors—skin type, sunburn history, lighter eyes and hair

- **Results:** Highest risk factors correlated with the BsmI polymorphism in the Vitamin D receptor almost 2:1

Hot off the Press: New Label for Sonidegib

- Label reflects long-term sustained response of BCC
- BOLT Trial: n=194 locally advanced BCC, 36 metastatic
  - 200 mg/d vs 800 mg/d
  - Objective response rate for 200 mg dose: 56%
  - Sustained median duration of response: 26 months
  - 30% experienced side effects that lead to discontinuation
No risk of rebound SCC with treatment of BCC with Hedgehog Inhibitors

- Retrospective Cohort: 1675 patients treated in early phase studies

- No evidence of increased risk of subsequent development of SCC (adjusted hazard ratio, 0.57; 95% confidence interval, 0.28-1.16).

- Covariates: age, sex, history of previous NMSC, and number of visits per year

Can AK treatment be simple yet complete…

- Veterans Affairs Keratinocyte Carcinoma Chemoprevention (VAKCC) trial
  - 12 VA medical centers recruited from 2009 to 2011 and followed up until 2013
  - 932 veterans with 2 or more AKs
  - Mean follow-up duration was 2.6 years

- “A single course of 5% fluorouracil cream effectively reduces AK counts and the need for spot treatments for longer than 2 years.”

Is “Spot Treating” better than “Not Treating?”

- 5% FU cream, (n = 468), or vehicle cream (n = 464) to the face and ears bid for 4 weeks
- At 6 months 5-FU group demonstrated:
  - fewer AKs compared with the control group
    - (3.0 vs 8.1, P < .001)
  - higher complete AK clearance rates
    - (38% vs 17% at 6 months)
  - fewer spot treatments at 6-month intervals, at and in between study visits during the trial (P < .01 for all)

Ingenol Disoxate (LEO 43204) 0.018% and 0.037%: Ester of Ingenol for Treatment of AKs

- Currently in trials for full face, scalp, and chest—3 day rx with 12 month F/U for recurrence
- More potent activation of protein kinase C
- Significantly more exuberant neutrophil bursts
- Superior antitumor effect in B16 mice with melanoma
- Improved stability at ambient temps

# Imiquimod 5% vs. 5-FU 5% vs. Cryo

<table>
<thead>
<tr>
<th></th>
<th>Imiquimod (n=26)</th>
<th>5-FU (n=24)</th>
<th>Cryosurgery (n=25)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Clearance</td>
<td>85%</td>
<td>96%</td>
<td>68%</td>
<td>p=.03</td>
</tr>
<tr>
<td>Histological Clearance</td>
<td>73%</td>
<td>67%</td>
<td>32%</td>
<td>p=.03</td>
</tr>
<tr>
<td>Sustained Clearance of Cleared Lesions All patients</td>
<td>73%</td>
<td>54%</td>
<td>28%</td>
<td>p&lt;.01</td>
</tr>
<tr>
<td>Sustained Field Clearance All patients</td>
<td>73%</td>
<td>33%</td>
<td>4%</td>
<td>p&lt;.01</td>
</tr>
<tr>
<td>Cosmetic Outcome (excellent)</td>
<td>81%</td>
<td>4%</td>
<td>4%</td>
<td>p&lt;.0001</td>
</tr>
</tbody>
</table>

New 4% 5-FU cream in Peanut Oil

- Aqueous vehicle cream w/ peanut oil, apply once daily
- 4 wk comparison study against 5% 5-FU bid, n=841

**Results:**
- All in 4% arm achieved 75% clearance (vs. 95%)
- 80% were 100% clear (vs. 75% for 5% 5-FU)
- 30% irritation in 4% cream arm compared to 60% in 5% arm
- Same comparison of stinging, crusting, and itching

*Peanut Oil added moisturizing effects and was safe to use in pts with peanut sensitivity.*

Dohil, M, “4%” *J Drugs Dermatol,*
Combining Calcipotriol and 5-FU

- Combination cream of both superior to 5-FU alone
- Induction of TSLP results in recruitment of anti-tumor T cells
- 131 pts applied combo or 5-FU alone bid for 4 days
- 8 weeks after: combo 87% mean AK reduction vs. 26% 5-FU
- Face, scalp, and upper arms also tested
- Higher incidence burning and erythema in combo group
  - 39% combo group vs. 13% 5-FU alone
- Concerns: stability of combo, treatment time, AEs

What’s coming for AKs

- **KX2-391 Ointment**
  - inhibit T cell migration and endothelial tubule, lymphocyte infiltration, angiogenesis

- **VDA-1102 Ointment**
  - Placebo vs 5% vs 10% for 28 d
  - anti-neoplastic agent
  - selective modulation of VDAC/HK2, unique to glycolysis and mitochondrial
  - selectively triggers apoptosis in cancer cells

- **SR-T100 gel--antiproliferative**
  - Solanum lycocarpum alkaloidic extract and their constituents, solamargine and solasonine
  - 16 week treatment study, 8 wk F/U for recurrence evaluation

- **Actikerall (LAS41005)**
  - 0.5% 5-fluorouracil (5-FU) and 10% salicylic acid in film-forming base
  - Comparison trial against placebo and LAS106521 similar compound
Management Strategies

- Start slowly
- Wait at least a week after cryotherapy
- Consider regions instead of full face
  - Forehead MWF
  - Rest of face TuThSat
- Make sure there is no history of HSV labialis
- Bacteriostatic healing ointment
- Barrier restoration
- Pramoxine lotion
- Mix equal parts with moisturizer to maximize surface areas
- Spray sunscreens
- *Turn the radio up or down but not off*
Tips for Success

- Have patients fill prescriptions between Monday to Thursday—less likely to be switched than Fridays or weekends.
- Have patients start treatments on Sundays so that reactions occur mid week rather than on weekends.
- Take at least 4-7 days off before and after destructions or surgery.
- Use every adjunct possible except steroids.
Chemoprevention with PDT is not old news but should be routine


### TABLE 2. Median Squamous Cell Cancer (SCC) (Invasive and in Situ) Lesion Counts and Reductions (Before and After Cyclic Photodynamic Therapy)

<table>
<thead>
<tr>
<th>Assessment</th>
<th>SCC Lesion Count, Median (96.1% CI)</th>
<th>Reduction from Baseline, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 months before treatment</td>
<td>20.0 (15.0–24.0)</td>
<td></td>
</tr>
<tr>
<td>12 months after treatment</td>
<td>4.0 (3.0–5.0)</td>
<td>79.05 (73.3–81.8)</td>
</tr>
<tr>
<td>24 months after treatment</td>
<td>1.0 (0.0–2.0)</td>
<td>95.0% (87.5–100.0)</td>
</tr>
</tbody>
</table>

CI, confidence interval.
Does Blue Light PDT using 20% ALA Reduce Occurrence of AK in high risk patients: 52 wk study.

- Submitted as abstract 5194
- Multi-center evaluator-blinded, placebo-controlled study
- Measures occurrence of AKs and development of NMSC subsequent to cryotherapy then multiple treatments with ALA-PDT
  - N=166, facial AKs, a history of NMSC, and histologic evidence of dysplasia within clinically normal-appearing perilesional skin.
  - Clinically evident facial AKs were treated with cryotherapy prior to initial PDT, randomly assigned to ALA-2X: (Baseline, Week 4); ALA-3X (Baseline, Week 4, Week 24) or VEH-PDT
  - Placebo treatments matched 1:1 to the two active groups.
Treatment Day

- Remind patients to bring a wide-brimmed hat to shield the treated lesions from ambient light.
- Bring books, music, or something to pass the time.
- Put together a package:
  - Topical anesthetics: lidocaine gel, pramoxine
  - Moisturizers, Sunscreens
- There is no reason to stop meds that are sensitizing in the UV spectrum since PDT works in 410-417nm
  - Antibiotics, Diuretics, Anti-hypertensives
  - *If you are worried, then have them hold the drugs on the day before and the day of treatment*
Tips from Dr. Andrea Willey: “spa experience”

- mild exfoliating wash
- glad wrap
- thermal spray
- hand cooler

- heat mask
- heat pad
- space heater

- paper
- pillow case
**Rationale for Antihistamines**

- Anticipated ALA PDT Response: erythema and edema
  - Edema generated by mast cell degranulation
  - Erythema response is unaffected by H1 blockade
  - More mast cell related over 72 hours than lymphocytic, so steroids not as potentially helpful

- New trial underway to measure LSRs
  - Randomized, Double-blind, Placebo-controlled, 5-20 AKs
  - 20 pts, given Cetirizine 10 mg or placebo prior to and after treatment
  - Measure LSRs: erythema, edema, crusting, exudation, vesiculation/pustulation and erosion/ ulceration

Return of Red: 10% ALA in nanoemulsion BF-200 (Ameluz®)

- 7.8% ALA free acid equivalent to 10% ALA
  - Spectrum around 630 nm
  - No PpIX induction below the basal membrane
  - European studies: emitting light between 580–1400 nm
  - Nanotechnology optimizes the transport of 5-ALA through the Stratum Corneum

Nanoemulsion Delivery of BF-200 allows penetration of ALA without permeation into dermis.
Return of Red: 10% ALA in nanoemulsion gel
Phase III pivotal trials

- 779 patients skin type I-II
- 4 to 8 AKs
- BF-200 10% gel vs. MAL 21.3% vs. Placebo
- narrow emission LED lamps 630 nm

BF-200 10% nano-ALA: Phase III Field treatment efficacy

- Over 60% of the patients were completely cleared after only one PDT
- Over 90% patient complete response was reached with a maximum of two PDTs
- No new safety issues became apparent with filed treatment

Pros and Cons of medical options for NMSC

Pros

- Plenty of non-surgical patients:
  - Anticoagulants
  - Oxygen
  - Nursing home/Non-ambulatory
  - Issues with Anesthesia
  - Surgical Fatigue (no más por favor)

- Bad Locations
  - Eyelids
  - Ears
  - Genitals
  - Multiple

Cons

- Expensive
- Off-label or not covered…or both
- Margins not defined
- Overall lack of experience and regimens in the derm world
- Pharma will not support it
- Recurrence and relapse data not completely published
What actually works for treating NMSC?

- Most every agent for treating AKs has been investigated for treating BCC, only imiquimod is FDA approved for sBCC

- Topical treatments for SCC still do not relieve or mitigate the risk of invasion or metastasis

- Is the concept of a non-surgical option even possible anymore? Aside from efficacy, what about liability?
If you were a skin cancer, and want to be successful, you would...

- Try to evade the host's inflammatory mechanisms and take advantage of immunosuppression
- Recruit your own blood supply from the host to sustain growth
- Maintain and accelerate unregulated cell division to outgrow host defenses
- Become as immortal as possible to counter host apoptosis and death enzymes
Move over Antibiotic Resistance...

REVIEW

Resistance of Nonmelanoma Skin Cancer to Nonsurgical Treatments. Part I: Topical Treatments

T. Gracia-Cazaña, a,b,* S. González, c,d Y. Gilaberte b,e

a Unidad de Dermatología, Hospital de Barbastro, Barbastro, Huesca, Spain
b Instituto Aragonés de Ciencias de la Salud, Zaragoza, Spain
c Servicio de Dermatología, Memorial Sloan-Kettering Cancer Center, Nueva York, EE. UU.
d Departamento de Medicina, Universidad de Alcalá, Alcalá de Henares, Madrid, Spain
e Unidad de Dermatología, Hospital San Jorge, Huesca, Spain
Checkpoint Inhibitors for NMSC

- Programmed Cell Death proteins on T-cells → PD-1
  - PD-1 binds ligand PD-L1 on tumor cells blunts immune response
  - Monoclonal Abs (Pembrolizumab) target and block this interaction
- Cemiplimab (REGN2810) -- FDA Breakthrough Designation for Advanced Cutaneous SCC
  - EMPOWER-CSCC 1, Phase 2, potentially pivotal, single-arm, open label clinical trial of Cemiplimab
  - enrolling for metastatic or locally advanced unresectable CSCC.
Various Targets for Therapy

- **Mitogen-Activated Protein Kinases (MAPKs) Raf/ERK**
  - most critical mediator of Ras-dependent carcinogenesis
  - Activated Akt promotes cell survival by inhibiting apoptosis and regulates activation of NF-κB and AP-1

- Adding MEK inhibitors (cobimetinib, trametinib) helps combat tumor resistance
  - Demonstrated in melanoma, still investigated in SCC

Resistance to Topical 5% 5-FU
No controlled studies for 0.5%, 1%, or 4%

- 31 pts with sBCC--5% 5-FU bid for 11 weeks:
  - 90% histologic clearance, as early as 3 wks
  - 10% “tumor resistance” reported within 3 months
- 29 pts with SCC in situ--5% 5-FU bid for 4 weeks
  - Complete response rates fall: 83% at 3 months, 60% at 12 months
  - 17% recurrence after one year
- Theories behind resistance:
  - Dihydropyrimidine dehydrogenase (DPD)
  - Protein deficiencies: Bag-1, Hsp-70
  - Stem Cell proliferation during tumorigenesis
Imiquimod 5% cream vs excisional surgery (4 mm margin) of nodular or superficial BCC

- 401 (80%) pts intention-to-treat group year 3
- At 3 years, 178 (84%) of 213 pts cleared with imiquimod group vs 185 (98%) of 188 participants in the surgery group (RR 0.84, 98% CI 0.78-0.91; p<0.0001).
- No clear difference in cosmetic outcomes
- No treatment AEs, 12 pts imiquimod group withdrew due to reactions

PDT vs Imiquimod vs 5-FU for treatment of sBCC

- 7 centers in Netherlands, n=601:
  - MAL-PDT; two sessions with interval of 1 wk
  - Imiquimod cream daily, 5x/week for 6 weeks
  - 5-FU cream bid for 4 weeks
  - Follow-up was at 3 and 12 months post-treatment

- MAL-PDT: 144/196 pts 72.8% (95% CI 66.8-79.4)
- Imiquimod: 158/189 pts 83.4% (78.2-88.9)
- 5-FU: 159/198 80.1% (74.7-85.9)

Put the debate to rest…

Three-Year Follow-Up Results of Photodynamic Therapy vs. Imiquimod vs. Fluorouracil for Treatment of Superficial Basal Cell Carcinoma: A Single-Blind, Noninferiority, Randomized Controlled Trial

Marieke H. Roozeboom¹,², Aimee H.M.M. Arits¹,²,³, Klara Mosterd¹,², Anja Sommer⁴, Brigitte A.B. Essers⁵, Michette J.M. de Rooij⁶, Patricia J.F. Quaedvlieg⁷, Peter M. Steijlen¹,²,³, Patty J. Nelemans⁸,⁹ and Nicole W.J. Kelleners-Smeets¹,²,⁹
PDT vs. 5-FU-vs. Imiquimod for BCC

- 3 year follow-up: MAL-PDT, Imiquimod 5%, and 5% 5-FU
- 590 patients treated, 66 treatment failures within three years
Ingenol Mebutate gel and BCC

- PEP005 0.0025%, 0.01% and 0.05% Gel With Two Treatment Schedules, Day 1 & 2 or Day 1 & 8
- sBCC 4-15 mm, nBCC <4mm thick
- Australia 60 pts, bx proven nBCC on face, scalp, or body
- Efficacy and cosmetic outcome assessed at day 85
- sBCC study:
  - Histological clearance occurred in five of eight patients (63%) randomized to ingenol mebutate gel, 0.05% in Arm A.
  - Efficacy appeared to be dose-related, better outcomes with daily than once per week
  - 6 pts severe responses, one severe beyond application site

Ingenol Mebutate 0.05% gel and SCC in situ

- **24 pts**, two applications of 0.05% PEP005 gel on the extremities, trunk or face.
- Return for check-up visits the day after the first application and routine milestones x 2-3 months

Iningenol Disoxate (LEO 43204) 0.018% and 0.037%: Ester of Ingenol for Treatment of AKs

- Currently in trials for full face, scalp, and chest—3 day rx with 12 month F/U for recurrence
- More potent activation of protein kinase C
- Significantly more exuberant neutrophil bursts
- Superior antitumor effect in B16 mice with melanoma
- Improved stability at ambient temps

What works for SCC *in situ*?

- **Topical 5% 5-FU**
  - 26 pts, applied bid for ~9 wks
  - Complete clearance up to 55 mo

- **5% 5-FU vs. ALA-PDT**
  - Daily for 4 weeks vs. one or two cycles
  - 12 months after treatment:
    - 5-FU 48% clearance
    - PDT 82% clearance

- **Imiquimod 5% cream**
  - 31 pts, treated qd for 16 weeks
  - All resolved with clearance up to 9 months

- **Erythroplasia of Queyrat:**
  - Imiquimod doses ranged from 3x/wk to once daily for anywhere from 4 to 24 weeks resulted in clearance

- **Extramammary Paget’s disease**
  - Imiquimod: Adjuvant to surgery
  - Topical 5-FU: few case reports as monotherapy
Dobesilate 2.5% and 5% gel
- Inhibition of Fibroblast Growth Factors (FGF) upregulated in cutaneous tumors
- Impairs proliferation and angiogenesis
- Stinging and burning on first applications
- Efficacy data down the road

Betulinic Acid
- Purified from bark of Birch Trees
- Pentacyclic Triterpenes—direct anti-mitochondrial effects lead to cytotoxicity and promotion of apoptosis
- Ointment based Triterpenes tolerated in AKs awaiting trials for BCC and SCC in situ

Stay Away Skin Cancer...

- Photolyases—sunscreen based
- Polypodium leucotomos extract
- Nicotinamide
- Photodynamic Therapy
- Retinoids
- NSAIDs
- Caffeine
Photolyases

- Naturally occurring enzymes
  - Repair UV-induced thymidine dimers
  - Absent in placental mammals
  - Active in organisms with high cumulative UV exposure.
  - Exogenous forms isolated from a cyanobacterium *Anacystis nidulans* in marine plants

- Long-term use improves:
  - Expression of MMP-1, Ki67, PCNA
  - Mutations of p53, p21

Photolyases Provide Protection Post-PDT

- Sunscreens contain Photolyases encapsulated in liposomes
  - 36 pts, scalp AKs, treated with PDT; biopsies performed pre-PDT, after one month and one year use,
  - Overall reduction of p53 expression (indicative of apoptosis cell) and Ki67 expression in comparison with a sunscreen with SPF 50+

Preventative effects of photolyases compared to conventional sunscreens

- 9 month long study involving 30 patients after treatment with PDT on the face or scalp
- Sustained remission of previously treated AKs and in patients treated once with PDT
- All patients in the group treated with photolyases avoided a second PDT treatment vs. 10 of 15 subjects in the sunscreen only group needing a second treatment to stay clear
Long-term prevention strategy with exogenous photolyases in sunscreens

- Study with Xeroderma Pigmentosum n=8
  - inherited defects in nucleotide repair mechanisms and ongoing formation of CPDs
  - Treated for at least 12 consecutive months
  - 65% reduction in appearance of new AKs
  - 56% BCC and no new SCC

Patients with XP in split study: Differences in the mean rate of production of AK and NMSC over a one year treatment time with sunscreen containing photolyases.

Polypodium leucotomos Extract: Yes it is natural but what is the dose?

- Marketed OTC as a food supplement: 240 mg capsule
  - Antioxidant effects through polyphenolic acids
- Use for daily photoprotection is different than incorporation into a treatment regimen
  - One capsule daily, add one before sun exposure
  - Higher doses~480-960 mg for treating vitiligo, melasma, and PMLE
- New data: patients with lighter skin types could benefit from more photoprotection from an extra dose than darker patients
  - “Measurable suppressive effects on UVB-induced erythema”

Polypodium leucotomos Extract for Chemoprevention? So far only data in mice

- PLE in UV-irradiated mice delays tumorigenesis
  - Increases epidermal p53 expression and the anti-oxidant status of UV-irradiated hairless mice
  - In non-tumoral skin, this increase was significantly higher in PL-treated animals than in non-treated mice
  - Can contribute in delaying tumor development, either by repairing the damaged DNA or by increasing apoptosis

- Studies coming for chemoprevention in humans?

Nicotinamide 1000 mg daily ($10/mo)

- Phase 3 ONTRAC skin cancer prevention study
  - N=386 pts, aged 30-91 years, hx ≥2 NMSC over past 5 years
  - Reduced incidence of new skin CA by 23% vs. placebo after 1 year among high risk patients
  - Reduced new AKs by 11% at 3 months, 15% after 12 months
  - Prevents UV-induced ATP depletion, glycolytic blockade
  - Enhanced DNA repair
  - Reduces UV-induced immunosuppression

- No vasodilatory side effects: HA, flushing, itching, hypotension

Good News and Bad News on using Retinoids for Chemoprevention

- **Good News:**
  - Retinoids stabilize differentiation and atypical keratinocyte replication
  - Inhibit of ornithine decarboxylase
  - Promote of dendritic cell activity and restoration of apoptosis

- **Bad News:** Good luck finding a way to get them for your patients
  - But if you can: Start slow 10 mg acitretin daily and increase as tolerated, 25 mg qod then qd
  - Titrate up and down to manage side effects…but don’t stop
  - Every systemic retinoid is considered off-label for chemoprevention

Caffeine

- Oral ingestion: strong inhibitory effect on UVB-induced carcinogenesis
- Topical caffeine to the dorsal skin of mice pretreated with UVB for 20 wks resulted in enhanced apoptosis

<table>
<thead>
<tr>
<th>Exp.</th>
<th>Treatment</th>
<th>Tumors per mouse</th>
<th>Percent decrease</th>
<th>Tumors per mouse</th>
<th>Percent decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Water</td>
<td>4.00 ± 0.47</td>
<td>–</td>
<td>1.82 ± 0.30</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Oral caffeine</td>
<td>1.70 ± 0.48²</td>
<td>57</td>
<td>0.63 ± 0.31²</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>Acetone</td>
<td>7.07 ± 1.27</td>
<td>–</td>
<td>1.18 ± 0.25</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>Topical caffeine</td>
<td>3.93 ± 0.74²</td>
<td>44</td>
<td>0.33 ± 0.12²</td>
<td>72</td>
</tr>
</tbody>
</table>

In Experiment 1, UVB-pretreated high risk SKH-1 mice (30/group) with no observable tumors were given caffeine (0.44 mg/ml) as their sole source of coffee, expressed as the mean ± S.E. In Experiment 2, high risk UVB-pretreated SKH-1 mice (30/group) were treated topically with 100 μl acetone or caffeine (4 weeks). Each value represents the mean ± S.E.

*p<0.01 (Taken from refs. 5, 7)*

Green Tea Extract (Polyphenols) Derivatives for Chemoprevention

- DNA repair mediated through IL-12 induction
  - anti-photocarcinogenic activity when green tea added through drinking water in mice models
  - Targets for polyphenols: Ras oncogene, activator protein-1 (AP-1)

- Potential additives to sunscreens or other topical agents
  - Epigallocatechin gallate (EGCG)
  - Perillyl alcohol from limonene
  - DFMO ornithine decarboxylase inhibitor
  - selenium, retinoids and salicylates

Switch from liquor to coffee to reduce NMSC

- Meta-analyses: 241 NMSC cases (942 BCC and 3299 cSCC) cases
  - 307 articles, 13 case-control and cohort
- For every 10-gram increase in ethanol intake per day, a positive association was found for both BCC and SCC
- Sparse data at higher alcohol intake levels
  - Meant to serve as public health message

- Relative risks for NMSC:
  - 0.96 for one cup of coffee
  - 0.92 for one to two cups
  - 0.89 for two to three cups
  - 0.81 for more than three cups of coffee per day, respectively
- Caffeinated coffee may have dose dependent chemopreventive effects against basal cell carcinoma


Not to be forgotten...

- **Sebaceous Carcinoma**
  - 3 cases/1 million people
  - Increasing frequency in males skin types I-II
  - *Increasing mortality in males skin type VI, extraocular tumor*

- **Dermatofibrosarcoma protuberans**
  - 0.41/100,000 people
  - Higher incidences in black skin and females than in past
  - Increasing cases of males over 80 with tumors on head

- **Merkel Cell Carcinoma**
  - **Avelumab**
  - CDK 4/6 inhibitor of PD (programmed cell death pathway)
  - 88 pts studied—33% complete or partial shrinkage
  - 6 months—86% sustained clear, 12 months—45% sustained

- Similar studies with **Pembrolizumab**

Jeremy Bordeaux derm foundation
New Approaches to Cutaneous Oncology

- Revival of topical Nitrogen Mustard
- Topical Hypericin plus UVB—localized photodynamic tx
- Systemic options revisited: Bexarotene, JAK Inhibitors
- PD-1 Inhibitors for CTCL
- BRAF inhibitors for Langerhans Cell Histiocytosis
- Topical rapalogues for angiofibromas, Kaposi’s Sarcoma
- JAK Inhibitors for GVHD
Thank you