The Latest on 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: bhatiahabor@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
What is the destiny of an untreated AK?

- 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

Broad variation in transplant patients developing SCC from AKs

Table 1. Adjusted odds ratios with 95% confidence intervals for risk of squamous cell carcinoma in relation to incidence, regression, and overall change in actinic keratosis 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>Total no. of incident AKs</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>9.52 (1.60-56.70)</td>
</tr>
<tr>
<td>Total no. of regressed AKs</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>Overall change in AK counts</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>-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>3.77 (1.30-10.94)</td>
</tr>
</tbody>
</table>

Bold indicates results reaching statistical significance.
AK, Actinic keratosis; 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.

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

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
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.

Imiquimod 5 year recurrence

- Final results of a 5-year follow-up study
  - Evaluate the recurrence rate of sBCCs treated with imiquimod.
  - 163 (89.6%) of 182 patients resolved target sBCC at 12-week post-treatment assessment followed for up to 5 years.
  - 18 recurrences at the target site
    - 8 within 6 months, 10 at 12 months of follow-up
    - 5-year estimates of overall treatment success 77.9%
    - 80.9% histological success rate

Imiquimod 5% cream vs excisional surgery (4 mm margin) of nodular or superficial BCC

- Direct comparison of time to first recurrence and aesthetic appearance
  - Assess at 6 mo, 1 yr, 2 yr, and 5 years

- N=501 randomly assigned
  - Imiquimod group (n=254)
  - Surgical excision group (n=247)

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

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?

Just something natural please...

- 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 2

<table>
<thead>
<tr>
<th>Exp.</th>
<th>Treatment</th>
<th>Keratoacanthomas</th>
<th>Squamous cell carcinomas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tumors per mouse</td>
<td>Percent decrease</td>
<td>Tumors per mouse</td>
</tr>
<tr>
<td>1</td>
<td>Water</td>
<td>4.00 ± 0.47</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Oral caffeine</td>
<td>1.70 ± 0.48²</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>Acetone</td>
<td>7.07 ± 1.27</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>Topical caffeine</td>
<td>3.93 ± 0.74²</td>
<td>44</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 caffeine, 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 (0.44 mg/ml) for 6 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

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

Other Supplements to be aware of

Vitamin D

- PubMed database search
- 63 observational studies of vitamin D status in relation to cancer risk
- 30 colon, 13 breast, 26 prostate, and 7 ovarian cancer, assessed the association of vitamin D receptor genotype with cancer risk.
- **Protective relationship between sufficient vitamin D status and lower risk of cancer. Skin CA not isolated**

Selenium

- Deficiency decreases glutathione peroxidase and promotes early UV-induced increase in superoxide dismutase and catalase
- Causal linkage of low plasma selenium levels to increased risk of NMSC in humans.
- Study of hairless mice examined the dietary selenium level and carcinogenesis.
- UV doses of 90 mJ/cm², 3x/wk for 20 weeks, all groups developed skin CA.
- Following UV exposure course: incidence of tumors decreased for mice on 0.5 mg/kg of dietary Se.


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>95.0.0 (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.
Pearls on using Retinoids

- Start slow 10 mg acitretin daily and increase as tolerated, 25 mg qod then qd
- Titrate up and down to manage side effects
  - If considering women of childbearing age it might be easier to use isotretinoin due to its shorter half-life.
- Risks will rebound with discontinuation so treat with a routine to balance dryness, labs, and risks of alopecia and neuro effects with dose modification
- Watch expenses also, there is no endpoint…

# Systemic Chemoprevention for AK

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Type and Duration</th>
<th>No. of Patients</th>
<th>Acitretin Dosage</th>
<th>Treatment Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bavinck et al, 1995&lt;sup&gt;19&lt;/sup&gt;</td>
<td>RCT, 6 months</td>
<td>38</td>
<td>30 mg/day</td>
<td>Statistically significantly fewer patients with new skin cancers compared to placebo; reduction of number of actinic keratoses.</td>
</tr>
<tr>
<td>Yuan et al, 1995&lt;sup&gt;21&lt;/sup&gt;</td>
<td>NCG, &lt;6 to &gt;12 months</td>
<td>15</td>
<td>50 mg/day</td>
<td>Variable effects on skin cancer.</td>
</tr>
<tr>
<td>McKenna et al, 1999&lt;sup&gt;22&lt;/sup&gt;</td>
<td>NCG, 5 years</td>
<td>16</td>
<td>0.3 mg/kg/day</td>
<td>Statistically significant reduction of new skin cancers after 4 years compared to pretreatment period.</td>
</tr>
<tr>
<td>McNamara et al, 2002&lt;sup&gt;24&lt;/sup&gt;</td>
<td>NCG, 10 to 24 months</td>
<td>5</td>
<td>10 to 25 mg/day</td>
<td>3 patients, significant decrease in new tumors compared to pretreatment period; 2 patients, moderate decrease in new tumors.</td>
</tr>
<tr>
<td>George et al, 2002&lt;sup&gt;20&lt;/sup&gt;</td>
<td>RCT, 2 year</td>
<td>23</td>
<td>25 mg/day</td>
<td>Number of SCCs significantly lower on acitretin compared to drug-free period.</td>
</tr>
<tr>
<td>de Sévaux et al, 2003&lt;sup&gt;21&lt;/sup&gt;</td>
<td>RCT, 1 year</td>
<td>26</td>
<td>0.4 mg/kg/day vs 0.2 mg/kg/day</td>
<td>Decrease of actinic keratoses by 50% in both groups; no effect on development of skin cancers in both groups compared to pretreatment period.</td>
</tr>
</tbody>
</table>

**RCT** = randomized controlled trial; **NCG** = no control group; **SCC** = squamous cell carcinoma.

Chemoprevention for BCC: Radiation Therapy and Vismodegib for Advanced BCC

- Phase II single arm safety/efficacy, n=24
  - Combine radiation therapy after induction and concurrently with Vismodegib
  - Vismodegib 150 mg daily for 12 wks
  - Week 12 start XRT 30 min qD Mon-Fri x 7 wks along with Vismodegib until week 19

- Assess for control from therapy completion at 12 mo and 18 mo with absence of progressive disease and adverse events

Celecoxib in Preventing BCC in Patients With Gorlin’s Syndrome

- Phase II Randomized, Double-Blind trial
  - At least 5 prior BCCs AND 4 within the past year
  - Oral Celecoxib or placebo twice daily x 2 years
  - 60 pts total followed q 3 mo x 3 years
- Pts with <15 active lesions at baseline:
  - Celecoxib had a 20% increase in “total BCC burden” after 3 years compared to 50%
- Similar studies for AKs have been withdrawn or not completed

Capecitabine

- Antimetabolite for Colon, Rectal, Breast CA
- Study 1: 12 transplant pts, >6 invasive SCC/yr
  - Rx low-dose capecitabine (150 mg, 500 mg)
    - 1 mg twice a day for 2 weeks
    - repeated in 3 week cycles have been shown to reduce new SCC, but not BCC
- Study 2: 12 months pretreatment, decrease in the incidence of SCC in 10 pts treated with oral capecitabine; 57 total SCC