Extreme dermatoheliosis: How to approach the severely sun damaged patient

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I have no relevant conflicts of interest to disclose
Objectives

• Learn how to approach patients with field cancerization

• Combine known techniques to improve control rates and reduce field damage in patients with severe dermatoheliosis

• Utilize systemic therapy to slow down rate of formation of AK/SCCis/NMSC
The Clinical Challenge
This is easy
The Clinical Challenge
Field Cancerization
What is Field Cancerization?

• Concept introduced in 1953
• Cancer does not arise as an isolated cellular phenomenon, but rather as an anaplastic tendency involving many cells at once
Management of field change in actinic keratosis

M. Vatve*, J.-P. Ortonne†, M.A. Birch-Machin‡ and G. Gupta*

*Department of Dermatology, Monklands Hospital, Airdrie, Lanarkshire, U.K.
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‡Dermatological Sciences, Institute of Cellular Medicine, School of Clinical and Laboratory Sciences, Newcastle University, Newcastle upon Tyne, U.K.

Treatment of field cancerization with presence of multiple clinically visible AK

The presence of field cancerization indicates a high risk population with subclinical invisible disease, multiple primary tumours, local recurrences and premalignant change, which requires repeated treatments and causes significant morbidity. Currently site specific treatment with regular follow-up and screening for further tumours is the standard management. However, 25% of tumour resection margins of histologically proven AK show genetic alterations, which may be responsible for local recurrences. The field change may be as large as 7 cm around tumours, resulting in secondary tumours which are genetically similar. This is in contrast to a second primary tumour, which has an unrelated genetic pattern, is more than 2 cm from the first tumour and arises at least 3 years after the first tumour. Treatment should therefore target an area of field change which may reduce the risk of development of further AK, second tumours and local recurrence.

Scenario #1: Failed 5 fluorouracil
Mediocre cure rates with monotherapy

A randomised study of topical 5% imiquimod vs. topical 5-fluorouracil vs. cryosurgery in immunocompetent patients with actinic keratoses: a comparison of clinical and histological outcomes including 1-year follow-up

N. Krawtchenko, J. Roewert-Huber, M. Ulrich, I. Mann, W. Sterry and E. Stockfleth

Department of Dermatology, Charité, Skin Cancer Center Charité, University Hospital, Berlin, Germany

73 patients
Randomized to:
cryosurgery (20-40 sec/lesion up to 2 sessions 2 weeks apart
vs. 5% fluorouracil cream (twice daily x 4 weeks)
vs. Imiquimod 5% cream (three times per week x 4 weeks x up to 2 sessions with 4 week rest period between sessions)
Imiquimod and 5 FU had superior clinical & histologic clearance rates compared to cryotherapy.
<10% patients treated with cryotherapy remained clear after 12 months

Fig 2. (a) Recurrence rates of initially cleared lesions 12 months after end of treatment (EOT). n = 26, 24, and 25 for imiquimod (IMIQ), 5-fluorouracil (5-FU), and cryosurgery, respectively. p < 0.01.
(b) Sustained field clearance rates 12 months after EOT. n = 26, 24, and 25 for IMIQ, 5-FU, and cryosurgery, respectively. p < 0.01.
A randomized pilot comparative study of topical methyl aminolevulinate photodynamic therapy versus imiquimod 5% versus sequential application of both therapies in immunocompetent patients with actinic keratosis: Clinical and histologic outcomes

Carlos Serra-Guillén, MD,a Eduardo Nagore, MD,a Luis Hueso, MD,a Victor Traves, MD,b Francesc Meseguer, MD,a Onofre Sanmartin, MD,a Beatriz Elombar, MD,a Celia Requena, MD,a Rafael Botella-Estrada, MD,a and Carlos Guillén, MDa Valencia, Spain

Table IV. Local reaction at week 4 of treatment with imiquimod in patients treated with imiquimod as monotherapy and patients treated with photodynamic therapy and imiquimod

<table>
<thead>
<tr>
<th></th>
<th>Imiquimod (n = 33)</th>
<th>PDT + imiquimod (n = 32)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>8 (24%)</td>
<td>16 (50%)</td>
<td>.007</td>
</tr>
<tr>
<td>Moderate</td>
<td>11 (33%)</td>
<td>13 (41%)</td>
<td></td>
</tr>
<tr>
<td>Intense</td>
<td>14 (43%)</td>
<td>3 (9%)</td>
<td></td>
</tr>
</tbody>
</table>

TREATMENT OF ACTINIC KERATOSES WITH SEQUENTIAL COMBINATION OF 5-FLUOROURACIL AND PHOTODYNAMIC THERAPY

Dore J. Gilbert MD
Newport Dermatology & Laser Associates, Newport Beach, CA

Abstract
Actinic keratoses (AKs) are traditionally treated with cryotherapy, curettage, and 5-fluorouracil (5-FU, Efudex®, ICN Pharmaceuticals, Inc.), all of which are associated with adverse effects. Although photodynamic therapy (PDT) with topical 5-aminolevulinic acid (ALA) offers a treatment alternative, current protocols require 14 to 18 hours incubation with ALA and patients experience pain during light treatment. Fifteen patients with multiple and diffuse facial AKs applied 5-FU nightly for 5 days and underwent PDT with ALA (Levulan® Kerastick®, Dusa Pharmaceuticals, Inc.) on the sixth day. ALA was applied to their entire faces and remained in contact with the skin for 30 to 45 minutes under low-intensity visible light. After removing ALA, faces received a single pass of 560- to 1200-nm intense pulsed light (VascuLight or Lumenis One, Lumenis). At 1 month and at 1 year post-treatment, 90% of treated AKs had resolved in all but one patient. Erythema resolved 7 to 10 days after treatment. Patients with multiple diffuse AKs may benefit from the application of 5-FU for 5 days followed by ALA-PDT with intense pulsed light activation.
Prospective, Case-Based Assessment of Sequential Therapy With Topical Fluorouracil Cream 0.5% and ALA-PDT for the Treatment of Actinic Keratosis

George Martin, MD
Dermatology and Laser Center of Maui, Kihei, HI

**Patient 1**
Age 66, Fitzpatrick type I

**Patient 2**
Age 71, Fitzpatrick type II

**Patient 3**
Age 81, Fitzpatrick type III

**INITIAL TREATMENT**

**Patient 1**
- Face: Left Side
  - 5-FU cream 0.5%
  - once daily
  - for 7 days
- Face: Right Side
  - Untreated

**Patient 2**
- Forehead/Scalp: Left Side
  - 5-FU cream 0.5%
  - once daily
  - for 10 days
- Forehead/Scalp: Right Side
  - Untreated

**Patient 3**
- Left Arm
  - 5-FU cream 0.5%
  - once daily
  - for 7 days
- Right Arm
  - Untreated

**TREATMENT 2**

- Short-contact ALA-PDT (1-hour incubation) to entire treatment area; assess tolerability/response 3-4 days later

- Short-contact ALA-PDT (2-hour incubation) to both arms; assess tolerability/response 3-4 days later

**Follow-up: 6 and 18 months after diagnostic rechallenge**

**Diagnostic rechallenge with 5-FU cream 0.5%, once daily, for 7 days, to entire treatment area**
Our Protocol

Treatment of Field Cancerization on the Head & Neck

1. Day 0: Curettage of any hyperkeratotic actinic keratoses
2. Day 1-5: Topical 5 Fluorouracil 0.5% twice daily
3. Day 6: Photodynamic therapy with 1 hour incubation
Sequential Curettage, 5-Fluorouracil, and Photodynamic Therapy for Field Cancerization of the Scalp and Face in Solid Organ Transplant Recipients

Anokhi Jambusaria-Pahlajani, MD, MSCE, * Stephanie Ortman, MD, * Chrysalyne D. Schmults, MD, MSCE, † and Christine Liang, MD ‡

BACKGROUND Field cancerization with actinic keratoses and squamous cell carcinoma in situ (AK/SCCIS) represents a common therapeutic challenge in solid organ transplant recipients (SOTRs). These patients often show inadequate responses to methods traditionally used as monotherapy (e.g., topical chemotherapy).

OBJECTIVE To describe the clinical outcomes and feasibility of a sequential approach to treatment of field cancerization in SOTRs.

METHODS Four SOTRs with field cancerization of the scalp and/or face were treated using a sequential approach. Light curettage of hypertrophic lesions was followed by application of 5-fluorouracil 5% cream twice daily for 5 days and photodynamic therapy (PDT) with 1-hour incubation on day 6. Pain level during and after PDT was recorded. Photographs were obtained immediately before and after treatment and at follow-up appointments.

RESULTS All 4 patients tolerated this approach well and demonstrated excellent responses to treatment with complete or near-complete clinical resolution of AK/SCCIS lesions. Patients remained free of AK/SCCIS based on clinical examination 1 to 6 months after treatment.

CONCLUSION For SOTRs with field cancerization, sequential therapy represents a viable therapeutic regimen with good tolerability and durable clinical response. This approach warrants further investigation to determine which therapeutic combinations have optimal tolerability and efficacy.
Scenario #2: Failed combination therapy
Reduction in the Incidence of Squamous Cell Carcinoma in Solid Organ Transplant Recipients Treated with Cyclic Photodynamic Therapy

Andrea Willey, MD,*†‡§ Sheetal Mehta, MD,*† and Peter K. Lee, MD, PhD*

• 12 patients with 13-28 SCCis and invasive SCCs in a 12 month period were included

• Intervention: Blue light PDT with 1 hour incubation every 4-8 weeks for 2 years
## Results

### 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>

Cl, confidence interval.
Scenario #3: Field Cancerization on the Arms/Legs
1) Apply thick layer of topical 5 Fluorouracil*
2) Place unna boot on the extremity
3) Re-apply weekly until mild inflammation/ulceration seen (typically about 4 weeks)

* I like to curette hyperkeratotic AK’s prior to 1st application
BRIEF REPORT

5% fluorouracil chemowraps in the management of widespread lower leg solar keratoses and squamous cell carcinoma

Ben Tallon and Nicholas Turnbull

1Skin Dermatology Institute, 2Bay of Plenty District Health Board, Department of Dermatology, Tauranga Hospital, 3Pathlab Bay of Plenty, Tauranga, New Zealand; and 4Department of Dermatology, Chelsea and Westminster Hospital, London, UK
Systemic Toxicity from Occlusive Therapy with Topical 5-Fluorouracil: A Case Report and Review of the Literature

MICHAEL SARGEN, BA, KAROLYN A. WANAT, MD, ANOKHI JAMBUSARIA, MD, MSCE, MISHA ROSENBACK, MD, JOSEPH SOBANKO, MD, AND CHRISTOPHER J. MILLER, MD*

• 64 year old female with field cancerization on bilateral arms and legs

• Developed exuberant reaction to chemowraps after 2 cycles with systemic symptoms:
  – fevers to 102 F, chills, fatigue, diarrhea, SOB, “rash”, transaminitis

Systemic Toxicity from Occlusive Therapy with Topical 5-Fluorouracil: A Case Report and Review of the Literature

Michael Sargen, BA, Karolyn A. Wanat, MD, Anokhi Jambusaria, MD, MSCE, Misha Rosenbach, MD, Joseph Sobanko, MD, and Christopher J. Miller, MD*
60% absorption of 5 fluorouracil if skin is ulcerated

**TABLE 1. Signs and Symptoms of Systemic Toxicity with 5-Fluorouracil**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fevers and chills*</td>
<td>Myelosuppression</td>
</tr>
<tr>
<td>Nausea and vomiting*</td>
<td>Anemia</td>
</tr>
<tr>
<td>Diarrhea*</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Abdominal pain*</td>
<td>Neutropenia</td>
</tr>
<tr>
<td>Generalized pain and discomfort*</td>
<td>Liver toxicity*</td>
</tr>
<tr>
<td></td>
<td>Mucositis and stomatitis</td>
</tr>
<tr>
<td></td>
<td>Erythematous skin rash*</td>
</tr>
<tr>
<td></td>
<td>Hand–foot syndrome</td>
</tr>
</tbody>
</table>

*Signs and symptoms of 5-fluorouracil toxicity observed in our patient.\(^4,5\)

- May have dihydropyrimidine dehydrogenase (DPD) enzyme deficiency
Authors Proposed Revised Treatment Guidelines

1. Apply 5FU/Unna boot on Monday and remove Thursday or Friday
2. Repeat weekly until superficial erosions occur
3. If some areas ulcerate, but residual areas still require 5FU, can apply topical 5FU to those areas only twice daily without occlusion
4. Any patient that has systemic symptoms should be checked for DPD deficiency.
Scenario #4: Multiple invasive SCC’s on the arms and legs
# Intrallesional chemotherapy for nonmelanoma skin cancer: A practical review

Joslyn S. Kirby, MD, and Christopher J. Miller, MD

*Hershey and Philadelphia, Pennsylvania*

## Table II. Intrallesional fluorouracil

<table>
<thead>
<tr>
<th>References</th>
<th>Tumor type</th>
<th>Type of study</th>
<th>No. of tumors/patients</th>
<th>Tumor diameter /mean, cm</th>
<th>Drug concentration, mg/ml</th>
<th>Dose/mean, mg</th>
<th>No. of treatments /mean</th>
<th>Treatment frequency /mean, d</th>
<th>Total/mean dose/mean, mg</th>
<th>Care rate</th>
<th>Length of follow-up /mean, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kurtis and Rosen,12 1980</td>
<td>KA</td>
<td>Case series</td>
<td>3/3</td>
<td>0.8-1.3/1.0</td>
<td>50</td>
<td>NR</td>
<td>6-12/8.3</td>
<td>3</td>
<td>177.5-585/354</td>
<td>3/3 (100%)</td>
<td>NR</td>
</tr>
<tr>
<td>Goette and Odom,18 1980</td>
<td>KA</td>
<td>Case series</td>
<td>41/30</td>
<td>NR</td>
<td>50</td>
<td>NR; range, 40-75</td>
<td>NR/3</td>
<td>7</td>
<td>NR</td>
<td>40/41 (97.5%)</td>
<td>1-22/NR</td>
</tr>
<tr>
<td>Klein et al,19 1962</td>
<td>KA</td>
<td>Case series</td>
<td>2/2</td>
<td>NR</td>
<td>50</td>
<td>5</td>
<td>7-34/20</td>
<td>0.5-2/1.25</td>
<td>3.5-170/86.75</td>
<td>2/2 (100%)</td>
<td>NR</td>
</tr>
<tr>
<td>Singal et al,11 1997</td>
<td>KA</td>
<td>Case report</td>
<td>Numerous</td>
<td>0.1-2</td>
<td>50</td>
<td>10-15</td>
<td>3</td>
<td>7</td>
<td>30-45/NR</td>
<td>Numerous (100%)</td>
<td>NR</td>
</tr>
<tr>
<td>Leonard and Hanke,14 2006</td>
<td>KA</td>
<td>Case report</td>
<td>1/1</td>
<td>4</td>
<td>50</td>
<td>NR</td>
<td>8</td>
<td>7-14/NR</td>
<td>NR</td>
<td>1/1 (100%)</td>
<td>9</td>
</tr>
<tr>
<td>Eubanks et al,17 1982</td>
<td>KA</td>
<td>Case report</td>
<td>14/1</td>
<td>0.4-1.1</td>
<td>50</td>
<td>10-20/NR</td>
<td>5-9/NR</td>
<td>7</td>
<td>NR</td>
<td>14/14 (100%)</td>
<td>6</td>
</tr>
<tr>
<td>Parker and Hanke,18 1986</td>
<td>KA</td>
<td>Case series</td>
<td>5/4</td>
<td>2.2-6.0</td>
<td>50</td>
<td>50-150/NR</td>
<td>2-5/3.8</td>
<td>7</td>
<td>100-600/360</td>
<td>5/5 (100%)</td>
<td>18-45/30</td>
</tr>
<tr>
<td>Morse et al,19 2003</td>
<td>KA</td>
<td>Case report</td>
<td>1/1</td>
<td>3.3</td>
<td>50</td>
<td>40-120/80</td>
<td>8</td>
<td>7</td>
<td>680</td>
<td>1/1 (100%)</td>
<td>5</td>
</tr>
<tr>
<td>Total: 93/57</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>87/68</td>
<td>98.5%</td>
<td></td>
</tr>
</tbody>
</table>

*BCC, Basal cell carcinoma; KA, keratoacanthoma; NR, not reported.*
How I do it

- Divide tumor into quadrants
- Inject 0.1 ml 5 fluorouracil into each quadrant
- Max dose per session: 2 cc
- Repeat in 4-6 weeks as needed

- Note: Can shave to debulk (may decrease number of treatments)
Before-During-After
Scenario #5: Multiple invasive SCCs
Acitretin

• Exact mechanism unknown
  – Influences epidermal development and differentiation

• Used in chemoprevention of NMSC
Side Effects/Toxicity

• Teratogenicity*
• Dry eyes, photophobia
• Xerosis, retinoid dermatitis, PG, dry hair, telogen effluvium, paronychia, chelitis, dry mouth
• Arthralgias, myalgias, fatigue
• Hypercholesterolemia (increased TG → pancreatitis)
• Nausea, diarrhea, abdominal pain, transaminitis, Inflammatory Bowel Disease (UC > CD)
• Mild headache, Pseudotumor cerebri

* I do not give soriatane to women of childbearing age given conversion to etretinate
Prevention of Skin Cancer and Reduction of Keratotic Skin Lesions During Acitretin Therapy in Renal Transplant Recipients: A Double-Blind, Placebo-Controlled Study

By Jan N. Bouwes Bavinck, Linda M. Tieben, Fokko J. Van Der Woude, Adam M. Tegzess, Jo Hermans, Jan Ter Schegget, and Bert J. Vermeer

38 patients
>10 keratotic lesions on the hands/forearms

19 patients
Acitretin 30mg/day
6 months

19 patients
Placebo

6 month treatment free period
2 patients in treatment group vs 9 patients in placebo group developed NMSC in the 6 month treatment period.

Fig 1. Cumulative numbers of patients with new skin cancers (bars) and cumulative numbers of new skin cancers (lines) during and after retinoid intervention. The acitretin group (x and □) and placebo group (○ and △) both started with 19 patients.
Acitretin had the most benefit in patients with history of skin cancer

<table>
<thead>
<tr>
<th></th>
<th>History of skin cancer</th>
<th>No history of skin cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acitretin</td>
<td>1/9 (11%)</td>
<td>1/10 (10%)</td>
</tr>
<tr>
<td>Placebo</td>
<td>7/10 (70%)</td>
<td>2/9 (22%)</td>
</tr>
<tr>
<td></td>
<td>p=.009</td>
<td>p=.48</td>
</tr>
</tbody>
</table>
13.4% decrease in keratotic lesions in treatment group vs. 28.2% increase in placebo group (p=.008)
Practical Considerations

• Consider if pt had >5 invasive SCC’s in 12 month period

• Labs: Fasting lipids, CBC with diff, CMP
  – Baseline
  – Monthly x 2 months with each increase in dose

• Initial dose: 10 mg daily

• Goal dose: 25-30 mg daily (titrate to tolerability)
My General Approach

Biopsy anything that appears invasive

Treat appropriately

Field Therapy on AK/SCCis/Superficial SCC

Consider soriatane, decrease immunosuppression

No invasive Disease

Invasive Disease