Photodynamic Therapy 2016:
Light up the sky…
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Dr. Bhatia’s Disclosures:
- Affiliations with Actavis, Allergan, Anacor, Aqua, Bayer, Biofrontera, BiopharmX, Dermira, Dusa, Exelixis, Ferndale, Foamix, Galderma, Intraderm, ISDIN, LaRoche-Posay, Leo, Novan, Novartis, PharmaDerm, 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

The “Debate” gets more intense
- Resurgence of a Red candidate against the incumbent Blue
- New findings uncovered and leaked into the US
- Consolidation of the establishment against a new opponent with approaches to solve old problems

Cellular Responses to PDT
- Blue light (412-456 nm) is toxic to keratinocytes at high fluence (500 J/cm²)
- Nontoxic doses of blue light slow proliferation and induce differentiation markers in keratinocytes
- This may be due to nitric oxide generation
- Blue light is toxic to T cells
- Red light peak 635 nm
  - 37 J/cm² or 75 J/cm² of red light exposure to be effective
  - Targeting of sebaceous glands and P. acnes reduction
  - Curette probably enhances MAL penetration applied under occlusion for a period of 3 hours, followed by exposure to red light
- New evidence with 10% ALA of efficacy at deeper levels

What’s new in Red and Blue?
- 10% ALA nanoemulsion gel
  - FDA Approved May 2016
  - Paired with red light LED but efficacy proven with multiple lights
  - Studies for AK, BCC, and acne
  - Significant cosmetic outcomes
- Daylight and/or Blue?
- Warming beats cooling
- Microneedles and PDT
- Arms and Hands made easy
- New LED devices and treatment protocols on the way

Protoporphyrin IX Absorption Spectrum & Skin Penetration of Light
**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.

**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

**Photolyases Provide Protection Post-PDT**

- Photolyases—are absent in humans
  - Repair UV-induced cyclobutane pyrimidine dimers
- Reduce expression of p53 and Ki67
- 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+

**Randomized Vehicle-Controlled Study of Short Drug Incubation Aminolevulinic Acid Photodynamic Therapy for Actinic Keratoses of the Face or Scalp**

**Chemoprevention is not old news but should be routine**

**Daylight PDT may have its place but is not the new standard**
Painless PDT with 20% ALA—Maui Style

- 101 pts in safety/efficacy single site study
- 30-minute incubation → 1.5-2.5 hours of daylight exposure
- Short incubation minimizes PpIX accumulation prior to daylight
- Photobleaching prevents further buildup of PpIX post-treatment
- 3 subjects comparison arm: Split-face “painless PDT”
  - 3 subjects pre-treated for 7 days with 5-FU or Imiquimod
  - One side: 20% ALA field application without occlusion for 15 minutes then 60 minutes of continuous blue light activation
  - Other side: 75 min incubation/16m 40s Blue Light

Pearls from the Painless Protocol

- Subject’s faces were washed with gentle cleanser
- Eyes were covered with disposable opaque eye shields
- Post treatment: cool water-soaked facial cotton washcloth followed by clear aloe gel
  - Left wearing scarf, broad-brimmed hat, and sunglasses for 48 hrs
- Assessed one week post treatment
- Limited by weather on treatment day and patient cooperation

But Doc, it’s cold outside!: "Daylight PDT" June-Oct in Nordic Countries

- The mean lesion response rate at 3 months was approx. 75% for both 1½ and 2½ hr. exposure groups with Grade I AKs
- Treatment was well tolerated
- Patient Counseling:
  - “Subjects will be advised of the treatment requirements at the time of appointment booking and will be instructed to call the morning of their appointment to confirm that treatment can proceed."
- April to November:
  - “Weather conditions will be recorded on the day of treatment and final analysis will be stratified by temperature and weather conditions to evaluate whether this has impacted treatment."

Fractional Laser-assisted Daylight PDT vs Daylight PDT

- Norwegian study evaluating pretreatment with CO2 laser
  - Double-blind, 12 pts, organ transplants, > 5 AKs on scalp/face
- PDT: MAL under occlusion for 30 minutes before entering daylight for 2 hours
- Laser settings: 10mJ/cm², 120 micron tip/ablative columns with 5% density, fluence increased until onset of pain then reduced to maximum fluence without pain
  - pain used as a measure of penetration to dermis

Daylight PDT in the Northeast USA

- Newly submitted to assess feasibility in colder climate
- Study 1 yr and 5 yr clearance, underway until 2022
  - 40 pts, 20% ALA 30-60 min incubation then 2.5 hrs outdoors
  - Next 48 hours: minimize sun exposure; physical sunscreen and protective clothing
  - Assess in 1 mo, repeat unless completely clear
  - HSV prophylaxis valtrex 500mg daily for 3 days

www.ClinicalTrials.gov/NCT02867722
Daylight Photodynamic Therapy: The Southern California Experience

- More recently published, USA experience with ALA and expected sunny climate; N=80
  - Patients scheduled between 9-11am for ALA application
  - Mainly face, but also scalp, arms, dorsal hands, trunk
  - Curettage pre-tx for obvious AKs
  - ALA-PDT Protocol: 20% ALA, 60 min incubation, no occlusion
  - After 30 min, chemical sunscreen applied, no physical blockers
  - 2.5 hour daylight exposure (in shade)
  - F/U at 72h, 1 wk and 4-6 wks post-tx

- Results: Comparison to ALA-PDT w/ blue light
  - Results comparable, at 4-6 wks, subjective improvement in majority
  - Key difference: daylight PDT was not painful
  - Accessibility: ability to expose entire area to daylight without being cramped within blue light device or similar
  - Benefits of this protocol:
    - Pts were allowed for tx of scalp, ears, face, upper chest in one sitting, not possible in blue light device
    - Sunscreen applied AFTER ALA application (instead of other studies where sunscreen applied prior)
    - Vigorous responders healed well: no scarring or hypopigmentation
    - Pts w/ best outcomes had most significant reactions

Photodynamic Photorejuvenation with Microneedling, Red Light, and Broadband Pulsed Light

- Uncontrolled, pilot study, N=21
- Maximum of 4 non hyperkeratotic AKs and Facial photodamage
- ALA-PDT Protocol
  - Multiple passes with microneedle roller (steel solid bore needles, 108μm in width, 300μm in length)
  - 20% ALA solution for 1-hour incubation (without occlusion)
  - Pulsed light 560 nm, 3-5ms double pulse, 19-22J/cm²
  - LED red light illumination 75J/cm² (12 minutes)

- Results
  - Statistically significant differences between baseline and 3 & 6 mos post-treatment observed for all features except coarse wrinkles
  - *P<0.05 vs. Baseline, **P<0.05 vs. 3 Months Post-treatment

<table>
<thead>
<tr>
<th>Feature</th>
<th>Baseline</th>
<th>3 months</th>
<th>6 months</th>
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</thead>
<tbody>
<tr>
<td>Global Score</td>
<td>3.51±0.57</td>
<td>2.24±0.41*</td>
<td>2.09±0.47**</td>
</tr>
<tr>
<td>Fine lines</td>
<td>3.43±0.51</td>
<td>2.29±0.43*</td>
<td>1.98±0.26**</td>
</tr>
<tr>
<td>Mottled pigmentation</td>
<td>3.38±0.50</td>
<td>1.38±0.32*</td>
<td>1.33±0.31*</td>
</tr>
<tr>
<td>Roughness</td>
<td>3.24±0.58</td>
<td>2.19±0.40*</td>
<td>1.68±0.39**</td>
</tr>
<tr>
<td>Tactile roughness</td>
<td>3.62±0.66</td>
<td>2.14±0.39*</td>
<td>1.76±0.23**</td>
</tr>
<tr>
<td>Telangiectasia</td>
<td>3.33±0.66</td>
<td>2.33±0.39*</td>
<td>2.23±0.23*</td>
</tr>
<tr>
<td>Coarse wrinkles</td>
<td>3.19±0.48</td>
<td>3.04±0.83</td>
<td>2.90±0.23</td>
</tr>
</tbody>
</table>

RESULTS

Nineteen patients completed the trial and all follow-ups. The mean percentage reduction in ALA was 89.3% on the microneedled side versus 89.5% on the control side (significant difference, P < 0.05). The raw data of AK counts is presented in Table 1.

Our secondary objective of cosmetic improvement/enhancement was performed as physician's global assessment based on Visia camera images. In 18 of 19 patients, there was a noticeable cosmetic enhancement on one side of the face as compared to the other. In 13 of these 18 patients, the microneedled side was the enhanced side.

DISCUSSION

Certainly the first step in the successful performance of PDT is absorption of the Leukoxan into the viable epidermis where it is converted into the active metabolite protoporphyrin IX. It stands to reason the stratum corneum is the major obstacle to this absorption, and is only thinner in areas of acnelastic Frecklerkeratois. This study shows, in a statistically significant manner, that prior microneedling enhances

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**Return of Red: 10% ALA in nanoemulsion**

- 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


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**Nanoemulsion Delivery of BF-200 allows penetration of ALA without permeation into dermis**

BF-200

MAL

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**Return of Red: 10% ALA in nanoemulsion gel**

- 779 patients skin type I-II, 4 to 8 AKs
- BF-200 10% gel vs. MAL 21.3% vs. Placebo
- Treatment: illumination with either:
  - A) narrow emission LED lamps 630 nm
  - B) incoherent broad spectrum light sources:
    - emitting light between 580–1400 nm


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**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 (primary endpoint 12 weeks after the last PDT)
- No new safety issues became apparent with filed treatment

Trials in motion for 10% ALA gel

- Phase 3 Daylight PDT (protocol as documented in the Metvix® SmPC)
- Side-by-side intra-patient comparison with Metvix® in 4 centers in Spain and 4 centers in Germany
- 50 patients with up to 9 AKs on each side

- 10% gel with and without occlusion
- Approved for lesion-directed and field-directed AK
- Variable light sources
- Acne vulgaris
- Superficial or nodular BCC
  - face, scalp, trunk and extremities

ALA-BCC-CT008: Pivotal comparator-controlled Phase III trial for BCC

- Side-by-side inter-patient comparison with MAL (Metvix®)
- 281 patients with 1-3 non-aggressive BCCs up to 2 mm thick (outside H-Zone)
- 26 centers in Germany and UK
- 2 PDTs one week apart
- Primary endpoint: Complete clearance of all BCC lesions
- Stratification by tumor thickness
- 5-year follow-up post approval
### AE Comparison: 10% ALA Gel and 20% ALA Solution

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>10% ALA Gel</th>
<th>20% ALA Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe pain/ stinging/burning</td>
<td>&gt;30%</td>
<td>&gt;50%</td>
</tr>
<tr>
<td>Pain/ stinging/burning</td>
<td>92%</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>Erythema</td>
<td>50%</td>
<td>99%</td>
</tr>
<tr>
<td>Edema</td>
<td>35%</td>
<td>35%</td>
</tr>
<tr>
<td>Scaling/ crusting</td>
<td>*</td>
<td>73%</td>
</tr>
<tr>
<td>Tenderness</td>
<td>*</td>
<td>2%</td>
</tr>
<tr>
<td>Itching</td>
<td>34%</td>
<td>32%</td>
</tr>
<tr>
<td>Ulceration</td>
<td>*</td>
<td>4%</td>
</tr>
<tr>
<td>Bleeding/ hemorrhage</td>
<td>1%</td>
<td>4%</td>
</tr>
<tr>
<td>Hyper/hyperpigmentation</td>
<td>*</td>
<td>30%</td>
</tr>
<tr>
<td>Vesiculation/ Vesicles</td>
<td>12%</td>
<td>5%</td>
</tr>
<tr>
<td>Pustules</td>
<td>7%</td>
<td>4%</td>
</tr>
</tbody>
</table>

* Not directly comparable due to changes in MedDRA.

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### PDT Summary

- More pearls in workshop later this afternoon
- Assess available active ingredients, vehicles, devices and practical applications
- Understand rationale for therapy
- Choose patients wisely and avoid over-exposure