U083: Field Cancerization Therapies: Medical Dermatology and Beyond
American Academy of Dermatology
77th Annual Meeting
Washington, DC

Maria M. Tsoukas, MD, PhD
Associate Professor of Dermatology
Head and Residency Director
University of Illinois at Chicago
Email: tsoukasm@uic.edu
NO CONFLICT OF INTEREST

PDT research work awarded by:
- The American Society for Dermatologic Surgery
  Cutting Edge Research Grant

Advisory Board
- Biofrontera, Ameluz
Outline

- Field Cancerization Concept
- Therapies
- Combination Modalities
- Outcomes
Field Cancerization Concept

• Skin surrounding clinically evident Aks is at increased risk for possible precancerous changes and malignant transformation
• Field therapies: clinically evident and subclinical Aks
• Reduce NMSCa incidence
Topical Methods to Intensify PDT in AK/NMSCA treatment

PDT

Imiquimod
5- Fluorouracil
Diclofenac
Ingenol Mebutate
Topical Retinoids
Chemical Peels

Lasers

Electrosurgery
Curettage
Surgery
Radiotherapy
Occlusion
Vitamin D
Methotrexate
Cryotherapy
ALA-PDT

- ALA (Levulan/Kerastic Dusa)
- BF-200 ALA Ameluz; (Biofrontera AG, Leverkusen, Germany) - red light
- MAL Metvix/Metvixia (Galderma, Lausanne, Switzerland) - red light: AKs, BD, sBCC, nBCC
- Alacare (Spirig AG, Egerkingen, Switzerland) - red light, mild AKs
Dosimetry: Important Factors

Drug and light dose “reciprocity”?

- Light sensitizing agent
- Bio-distribution
- Incubation time
- Irradiation time point following drug delivery
- Absorption maxima of photosensitizer
- Irradiation wavelength
- Light dose (fluence)
- Light irradiance

PDT limiting factors

• PS and light penetration
  – BCC tumors > 0.4 mm had higher recurrence risk
  – PDT not recommended for nodular BCC >2 mm depth
• PDT: not recommended for Morphea type BCC
  and has less efficacy on pigmented BCC
• Location of BCC: H zone has poor responses

*B J Dermatol 2013: 169, 549-554
*JAAD 2007: 56, 125-143
PDT limiting factors

- Aks on face better response than extremities
- Hyperkeratosis
- Size/depth of lesion
- Tumor resistance
- Patient age (efficacy decreases with older patients)
- Prior radiotherapy
- Pain
  - Anatomic location
  - Lesion diameter

B J Dermatol 2013: 169, 549-554
JAAD 2007: 56, 125-143
Why patients may prefer PDT and what they want to know:

- Overall downtime
- Appearance of skin during course (0-7 days)
- Clinical response
- Long term cure rates
- Final cosmetic outcome
- Compliance
- Need for additional sessions
- Off Label treatment (e.g. acne)
- Discomfort
Solid Organ Transplant Recipients

- 40%: Aks in 5 years
- Malignancy:
  - Skin: 42%
  - Urogenital: 12%
  - Lymphoreticular: 7%
  - Gastrointestinal: 6%
  - Larynx 3%
  - Bronchus 3%
  - Others

% with Skin Ca

Years since transplant
**Recommended Dermatological Consult in SOTR**

*In all situations discuss management with transplant team*

<table>
<thead>
<tr>
<th>Case</th>
<th>Frequency</th>
<th>Contents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre Transplant</strong></td>
<td>Once</td>
<td>Hx, Education</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Full skin exam</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Report to Tx MD</td>
</tr>
<tr>
<td><strong>Post Transplant</strong></td>
<td>Yearly</td>
<td>Education</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Full skin exam</td>
</tr>
<tr>
<td><strong>In situ SCC</strong></td>
<td>Q 6 mo</td>
<td>Education</td>
</tr>
<tr>
<td>(Aks, Bowen's)</td>
<td></td>
<td>Full skin examination</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Field cancerization</em></td>
</tr>
<tr>
<td><strong>Early cutaneous</strong></td>
<td>Q 4-6 mo</td>
<td>Education</td>
</tr>
<tr>
<td><strong>carcinogenesis</strong></td>
<td></td>
<td>Full skin exam</td>
</tr>
<tr>
<td>1-4 NMSC/year</td>
<td></td>
<td><em>Field cancerization</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Surgical removal of invasive SCC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consider systemic retinoids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Notify Tx MD</td>
</tr>
</tbody>
</table>

*Christenson LJ et al, Derm Surg 2004: 30: 598*

*Swiss Clinical Practice for skin cancer in organ transplant patients Swiss Med WKLY 2009:139:29-30: 407*
## Recommended Dermatological Consult in SOTR

<table>
<thead>
<tr>
<th>Case</th>
<th>Frequency</th>
<th>Contents</th>
</tr>
</thead>
</table>
| Moderate cutaneous carcinogenesis | Q 2-4 mo  | Education  
Full skin examination  
*Field cancerization*  
Surgical removal of invasive SCC  
Initiate systemic retinoids  
Contact Tx MD  
Recommend reduced immunosuppression  
Consider switching to mTOR inhibitors |
| Severe cutaneous carcinogenesis | Q 1-3 mo  | Education  
Full skin examination  
Topical treatment of *Field cancerization*  
Surgical removal of invasive SCC  
Initiate systemic retinoids  
Contact Tx MD  
Recommend reduced immunosuppression |
“Intensified” PDT

- AK pretreatment with 5-FU followed by ALA PDT:
  Intensified PDT achieves better and longer lasting results than monotherapy

- Sequential ALA-PDT followed by topical imiquimod twice weekly for 16 weeks: combination therapy significantly more effective in AK eradication vs PDT alone

- Sequential chemical peels followed by ALA-PDT
  - Intensifying PDT (Studies directed by Dr. N Konnikov, IACD 2012)
AK Reduction: 5-FU-ALA PDT vs PDT (N=19)

Tsoukas et al, Derm Surgery 2017;43(9): 1170-1175
Imiquimod: Mechanism of Action

- Binds TLR 7
- Induces TNFa, IL6, IFNa
- Antiviral and antitumor
PDT - Imiquimod

• Recommended as Monotherapy:
  Application 2-5 applications /wk, X 2-16 wks
• ALA-PDT followed by imiquimod 2X/W for 16 wks
• Combined therapy: 89.9% lesion reduction vs 74.5% of PDT alone (JDD 2009, 8, 35-39)
• PDT X1 followed by imiquimod 3X/W, X 1 mo, if not complete AK resolution repeat topical imiquimod for 1 month
• JAAD 2012,66,131-137
• Biomed Res Int 2013, 1-5
Diclofenac-PDT

• Inhibition of PG production by inhibiting the COX2
• Standard: Topical application 2x daily x 60-90 days
• Aks and BD: COX 2 positive
• Pretreatment with Diclofenac followed by ALA PDT X1 higher efficacy than PDT alone
• Pain can be more significant in combination therapy

*J Derm Treat* 2009, 20,259-265
Ingenol Mebutate
Patients need to know:

- Application protocol
- Number of weeks
- Anticipated AE
- Management AE
- Recurrence rates
- Cosmetic outcomes
TREATMENT ALGORITHM FOR ACTINIC KERATOSES

- Tsoukas et al:
- Am J Clin Derm:
- (19)4: 543-557
Daylight PDT

Would natural light reverse photodamage?

- Attractive simplification of conventional PDT
- Patients spend less time in clinic
- Less painful
- PPIX absorption: 410, 505, 540, 580, 535 nm
- PPIX Activation 87% 380-495 nm, 10% 495-590 nm, 3% 590-750 nm
Daylight PDT Safety and Discomfort

- Sunscreen (not physical blockers)
- Less discomfort than LED–PDT and uncomfortable at the end of the exposure
- Less pain when light exposure starts 30 min after MAL application
- Weather dependent
- Efficacy not associated with high intolerance
- Even with straight exposure to sun the procedure is very well tolerated

JEADV: 2012; 26; 673-79
PDT in Acne Vulgaris

- ALA incubation: 1-4 hours
- Occlusion
- Activation with Blu U, PDL, IPLs, LEDs
- Red light more likely to promote sebaceous gland destruction
- Complete clearance is achieved after 2-3 sessions
- Discomfort during PDT
# PDT reaction management

<table>
<thead>
<tr>
<th>Before</th>
<th>Post 5-FU</th>
<th>Post PDT</th>
<th>3 Days</th>
<th>1 Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cool mist / Ice</td>
<td>Topical Mupirocin 2%</td>
<td>Hydroquinone</td>
<td>Systemic antibiotics</td>
<td>Systemic antivirals</td>
</tr>
<tr>
<td>TAC 01%</td>
<td></td>
<td>Moisturization/SPF</td>
<td></td>
<td>Specialty referral</td>
</tr>
<tr>
<td>Pain control</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Conclusion

• Field therapies: Useful tools in treatment and prevention of NMSCA
• Monotherapies or Combination
• Patient selection, education, close F/U