F066: Photodynamic Therapy in Medical and Aesthetic Dermatology

Improving Efficacy and Maintaining Safety of ALA-PDT

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NO CONFLICT OF INTEREST

PDT research work awarded by:
-- The American Society for Dermatologic Surgery Cutting Edge Research Grant
Advisory Board
-- Biofrontera, Ameluz
Outline

- Photodynamic Therapy – Challenges and Limitations
- Medical applications - high risk patients
- Combination field cancerization therapies
- Cosmetic approaches
- Future Goals
PDT Procedure

1. Photosensitizer
2. Skin preparation and application
3. Light exposure
4. Post treatment follow up and skin care
5-ALA ( USA )

- 20% ALA (Levulan, Kerastick®, DUSA Pharmaceuticals)
  - 2 sealed glass ampoules
  - 354 mg δ - ALA hydrochloride powder
  - 1.5 ml hydroalcoholic solvent
  - Crushed within the applicator, at the time of use
  - Hand shaken, 3 min, to dissolve δ - ALA

- 10% ALA gel, aminolevulinic acid hydrochloride (Ameluz®, Biofrontera)
  -- Direct application to skin
  -- Lesion and field directed
ALA-PDT

- MAL Metvix/Metvixia (Galderma, Lausanne, Switzerland) - red light: AKs, BD, sBCC, nBCC
- Alacare (Spirig AG, Egerkingen, Switzerland) - red light, mild AKs
Photosensitizers/ Protocols

- ALA: Hydrophilic, MAL: Lipophilic
  - No significant difference in AK and nBCC
- BF-200 ALA: nano-emulsion: stability and penetration
  - Compared to MAL in AKs: 78%-64% respectively
- Alacare /skin colored patch: occlusion
  - Better efficacy and superior to cryotherapy
- ALA-PDT: single session repeated q 4-12 weeks
- MAL-PDT: AK 1 session, BD and BCC 2 sessions 1 week apart, repeated 3 months
  - JEADV 2013;27:672-9
Light Sources

- Lasers, filtered xenon arc, metal halide or fluorescent lamps, LEDs, IPLs
- Blu U (DUSA) 417 nm
- Aktilite (Galderma) 630-635 nm
- Omnilux (Phototherapeutics Ltd)
- Rhodoled (Biofrontera)
- Higher efficacy when narrow band light sources are used
Light Sources

- Fractionation: discontinuous illumination
  - 2-3 hour intervals, similar or increased light dose
  - Permits tissue oxygenation during dark periods
  - Higher efficacy in sBCC, not in Bowen’s Disease

- Daylight PDT:
  - Efficient AK eradication, cost effective, less pain
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 Patient Selection

- **Indications**
  - 18-95 yo
  - Skin Types I-IV
  - Extensive Photodamage
  - Not good surgical candidates
  - Patient compliance

- **Contraindications**
  - H/o Porphyria
  - Photosensitivity
  - Active infectious disease
  - Pregnancy / Lactation
  - Photosensitizing Drugs
Why patients may prefer PDT and what they want to know:

- Overall downtime
- Appearance of skin during course (0-7 days)
- Discomfort
- Clinical response
- Long term cure rates
- Final cosmetic outcome
- Compliance
- Off Label treatment
Skin Clinical End Points

- Erythema
- Edema
- Scaling
- Eschar
- Post peel erythema
- Transient pigment changes
- Recurrence

If evidence of:
- Alopecia
- Scarring
- Temporary/Permanent pigment changes
Common Challenging Factors in ALA-PDT:

- Light and Photosensitizer penetration in skin
- Conversion of ALA to PPIX
- Target selectivity
- Lesion recurrence
- Need for repeated treatments
- *Discomfort*
Skin Preparation and Application

- Acetone scrubs

- ALA application
Skin preparation

- Gentle curettage
- Keratolytics, overnight occlusion
- Tape stripping, microdermabrasion
- Laser resurfacing
- Micro-needle technique
- More important when nBCC, BD and sBCC than AKs are treated
- Occlusion post application: standard practice in MAL rather than in ALA
Skin Ca Prevention
Opportunities for Innovation

“FIELD” THERAPEUTIC MODALITY WITH SELECTIVE TARGETING

- Medical: Treatment of AKs and NMSCA
- Aesthetic: Acne, warts, HS, photo-rejuvenation
Actinic Keratosis & Non Melanoma Skin Cancer

- Actinic Keratosis (AKs): Scaly growth induced by sunlight
- US: Second most common reason for clinic visit
- Adults over 40: Prevalence 40-60%
- Transformation to skin cancer: 0.1-10%
- AKs may potentially evolve to SCC and BCC

*Criscione VD et al, Cancer 2009: 115:11:2523-2530*
Solid Organ Transplant Recipients

- AKs and Bowen’s affect up to 40% of OTR by 5 years after transplant
- Average time to develop SCC after transplant less or equal to 9 years
- SCC to BCC ratio
  - General population: 1/4
  - OTR: 2/1 to 8/1
Population-Based Standard Incidence Ratios of Skin Cancer in Transplant Patients

- Squamous Cell Carcinoma (10 fold increase in mortality)
- SCC of lip
- Basal Cell Carcinoma
- Melanoma

- 40-250-fold increase
- 20 to 38-fold increase
- 10-fold increase
- 1.6 to 3.4-fold increase

Jensen et al JAAD 1999;40:17
Hartevelt Transplantation 1990;49:506
Lindelof et al BJD 2000;143:513
Braathen et al JEADV 2012: 1063-66
<table>
<thead>
<tr>
<th>Factors</th>
<th>General Population</th>
<th>Transplant Population</th>
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<tbody>
<tr>
<td>Increasing age</td>
<td>++</td>
<td>++++</td>
</tr>
<tr>
<td>Fair skin, light hair, light eyes</td>
<td>++</td>
<td>++++</td>
</tr>
<tr>
<td>Sun exposure</td>
<td>++</td>
<td>++++</td>
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<tr>
<td>History of previous skin cancer</td>
<td>50% risk of 2nd cancer</td>
<td>&gt;70% risk of 2nd skin cancer</td>
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</table>
Additional Risk Factors for Skin Cancer in Organ Transplant Patients

- Duration of immunosuppression
  - Longer = more

- Intensity of immunosuppression
  - Stronger = more

- HPV infection
  - Present = more

- CD4 lymphocytopenia and Th2 dominance
  - Lower = more

*M Kosmidis et al. J Immunotherapy 2010 E pub*
### 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>
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</thead>
<tbody>
<tr>
<td><strong>Pre Transplant</strong></td>
<td>Once</td>
<td>Hx, Education</td>
</tr>
<tr>
<td></td>
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<td>Full skin exam</td>
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<tr>
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<td>Report to Tx MD</td>
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<tr>
<td><strong>Post Transplant</strong></td>
<td>Yearly</td>
<td>Education</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Full skin exam</td>
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<tr>
<td><strong>In situ SCC</strong></td>
<td>Q 6 mo</td>
<td>Education</td>
</tr>
<tr>
<td>(Aks, Bowen's)</td>
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<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>
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<tr>
<td>1-4 NMSC/year</td>
<td></td>
<td><em>Field cancerization</em></td>
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<tr>
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<td>Surgical removal of invasive SCC</td>
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<tr>
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<td></td>
<td>Consider systemic retinoids</td>
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<td></td>
<td></td>
<td>Notify Tx MD</td>
</tr>
</tbody>
</table>

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*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

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<thead>
<tr>
<th>Case</th>
<th>Frequency</th>
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</thead>
</table>
| **Moderate**              | 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**                | 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 |

**cutaneous carcinogenesis**  
5-10 NMSC/year  

**Severe cutaneous carcinogenesis**  
>10 NMSC/year
ALPDT in AKs

- Clearance 65-90% with one session
- Sessions are repeated q 4 weeks with ALA or 3 months with MAL
- 2-3 sessions may lead to complete clearance
- One year clearance 80% following ALA-PDT x 2 sessions and 63-69% single session
- Cryotherapy may lead to comparable results
PDT for AKs:

- Efficacy reduced 10% on extremities vs face and scalp lesions - less thick lesions
- Less effective than cryotherapy
  
  _Br J Dermatol_ 2008; 158: 994-999

- ALA PDT: Similar or better efficacy comparing to imiquimod (moderate thickness AKs: 58% vs 37% thin AKs 72%)
  
  _JEADV_ 2009;23:1061-1065

- BF-200 ALA more efficacious with 1-2 sessions: 83-90% clearance _Br J Dermatol_ 2012;166:137-146

- Occlusion for ALA-PDT in upper extremities: higher efficacy _JDD_ 2012;11:12: 55-61

- Patients favor PDT due to shorter course of treatment and excellent cosmesis _Br J Dermatol_ 2011;164:429-433
PDT: Safe and efficient photo-chemoprevention

- ALA PDT did not affect SCC but reduced the reappearance of Aks in 2 year f/u
  - J Invest Dermatol 2006: 126: 569
- ALA-PDT x 2 (1 wk apart) significant preventive potential in AK recurrence especially in first 6 months
  - BJD 2010: 162: 171
- SOTR may benefit out of MAL- PDT session, achieving 12 month clearance 62% vs 35% in controls
  - Acta Derm Venereol 2006; 86: 25
- Cyclic ALA PDT every 4-8 weeks x 2 years resulted in 79% reduction and 95% reduction of SCCs in 12 and 24 mo f/u
  - Derm Surg 2010: 36: 652
- ALA-PDT is effective in preventing Aks and NMSCA
  - JDD 2012: 11: 593
- Field therapies play significant role in NMSCA prevention
Bowen’s Disease

- ALA and MAL PDT: Effective for lesional areas up to 3 cm
- MAL-PDT: 2 sessions, clearance up to 96%, one year recurrence as in conventional therapies (cl 68-71%)


- Digital, subungual and nipple BD, penile intraepithelial neoplasia (PIN)

*BJD* 2008;159: 1245-1266

- Areas at high risk for NMSCA and poor healing
- *Not the treatment of choice for invasive SCC*
Optimizing and potentiating PDT

Clinical practice: Applications
- Imiquimod
- 5 –FU
- Diclofenac
- Chemical Peels
- Fractional Photothermolysis
- Daylight PDT

Basic Science
- Vitamin D: Sato et al, JID 2007, 127, 925
Topical Methods to Intensify PDT in AK/NMSSCA treatment

- Imiquimod
- 5-Fluorouracil
- Diclofenac
- Ingenol Mebutate
- Topical Retinoids
- Chemical Peels
- Cryotherapy
- Lasers
- Electrosurgery
- Curettage
- Surgery
- Radiotherapy
- Occlusion
- Vitamin D
- Methotrexate
“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)
Imiquimod
AK Reduction: 5-FU-ALA PDT vs PDT (N=19)

Tsoukas et al, Derm Surgery 2017;43(9): 1170-1175
Diclofenac

Cell membrane phospholipids

↑

Arachidonic Acid

NSAIDS

COX-2

Diclofenac

PGE-2

↓

Inflammation

Tumor Angiogenesis

Tumor Cell Growth

Inhibits Apoptosis
TREATMENT ALGORITHM FOR ACTINIC KERATOSES


- Multiple AKs (>4-8 / cosmetic unit or per 20 cm²)
- Extensive photoexposure / photodamage
- AK recurrence Q 6 months
- High risk (e.g. Immunosuppressed)
- H/o NMSCA

Field-directed therapy*

Conventional photodynamic therapy
- In Office-one-day procedure
- Inadequate response with topicals
- Patient not compliant with previous topical therapies
- Shorter inflammatory face
- Excellent cosmetic outcome

Daylight photodynamic therapy
- Greater tolerability
- Less discomfort
- Comparable outcomes to C-PDT

Lesion-directed therapy

Topical therapy
- Reimbursement limitations
- PDT not available
- Patient preference
- Light/heat sensitivity

- 5-FU
  - Established treatment
  - Variety of vehicles and strengths

- Imiquimod
  - Less frequent dosing per week
  - Supplied in satchels

- Diclofenac
  - Gel combines diclofenac and hyaluronate sodium

- Ingenol mebutate
  - Shortest duration of treatment among topicals
  - Relatively rapid resolution of local reactions

- Piroxicam
  - Sunscreen contained in the formulation

*Treatment can also be comprised of a combination of both PDT and topical treatments
Acne Vulgaris

- ALA is selectively absorbed by the sebaceous glands
- ALA-PDT targets acne inflammatory lesions
- Effective: longer light wavelengths
- Uncomfortable

*JID* 2000;115:183-192
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>• Moisturization/SPF</td>
<td></td>
<td>• Specialty referral</td>
<td></td>
</tr>
<tr>
<td>• Pain control</td>
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</table>
Pain management

- Important Factors:
  - Number, size, anatomic location of lesions
  - Monitoring: Visual Analog Scale (VAS)
- The redder the area, the more pain experienced and the better the treatment outcome
- Ice, cool air, cool mist during and post PDT
- Topical capsaicin 0.1% 3-4 days prior to PDT
  - Sandberg et al, Acta Derm Venereol 2006;86: 404-408
- Nerve blocks
Incorporating PDT to practice

- Easy to perform / no additional staff required
- Training: simple, still needs to be very thorough
- Flexibility in light source application
- No significant space requirements
- Patient education/consultation: pre and post care
Incorporating PDT to practice

- AKs easier to approach than acne
- Follow up periodically if severe AKs and photodamage, history of NMSCA, Bowen’s Disease and chronic immunosuppression
  - Follow ups: 3, 6, 12 months
- Cost and reimbursement
  - Light source
  - Pre authorization contacting insurance, if indicated