Aesthetic Extender Symposium 2013

Photodynamic Therapy: The All Purpose Remedy

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Photodynamic Therapy

The use of toxic oxygen radicals (¹O₂) generated from photoactivated molecular species to achieve a therapeutic response.

Agenda

- Definition
- History
- Photosensitizers
- Light Dosimetry
- Photochemical reaction
- Mechanism of Action
- Light Sources
- Advantages/Disadvantages

History

- Light used as therapeutic agent for 3000+ years
  - Egyptian, Indian, and Chinese civilizations
  - Psoriasis, rickets, vitiligo, skin cancer
- Photodynamic therapy (PDT) developed within the last century

Photodynamic Therapy

History

- 1903 - Hermann von Tappeiner – Used eosin dye and light to treat skin cancer
  
  Coined “Photodynamic action”

- 1913 - Meyer-Betz – demonstrated generalized photosensitizing effects of systemic hematoporphyrin
  
  Hematoporphyrin – the active metabolite in porphyrias

Acute Photosensitivity - Hematoporphyrin

- 1913
- Injected 200mg of hematoporphyrin
- Pain and swelling within minutes
- Generalized photosensitivity lasted 2 months

History

- 1924 - 1961 – a series of studies show that tumor cells
  
  Preferentially absorb photosensitizer
  
  When exposed to light, these tumor cells die

- 1970 – Dougherty - Promotion of PDT
  
  Human trials on cutaneous cancer metastasis
**Photodynamic Therapy**

**History**
- 1990 - Kennedy et al. conducted clinical trials with the topically applied photosensitizer, 5-aminolevulinic acid (5-ALA).
- 1999 - FDA approval of topical 5-ALA and blue light for actinic keratosis.

**Introduction:**
**Process of Photodynamic therapy**
- Two individually non-toxic components brought together to cause harmful effects on cells and tissues:
  - Photosensitizing agent
  - Light of specific wavelength

**Simple Terms**
- Target lesion
- Photosensitizer
- Light source
- Interact with tissue oxygen

**Nature 2003, 3, 380.**
Introduction:
Type 1 and 2 Reactions


FDA Approved Photosensitizers

- Intravenous
  - Photofrin
  - Verteporfin

- Topical
  - 5-aminolevulinic acid (5-ALA) - 1999
  - Methyl aminolevulinate (MAL) - 2004

Drug Delivery

- Topical, oral, intralesional, and IV routes

Tumor Selectivity

- Once delivered intact to, or produced within, tissues, photosensitizers will leak or be transported to both normal and target tissues
- Compounds are taken up by most normal and malignant cells, but are retained longer in tumors and rapidly proliferating cells
Photosensitizer Absorption

- **Neoplastic tissue**
  - Low pH
  - Photosensitizer pooling – leaky neovasculature and poor lymphatic drainage create a stromal "vaccuum" in tumor tissue
  - Large macrophage population (>50%)

- **Inflammatory tissue**
  - Activated lymphocytes
  - Enhanced cellular proliferation
  - Increased vasculature

Ideal Photosensitizer

- Chemically pure
- High target selectivity
- Low normal tissue phototoxicity
- High absorption coefficient ($\mu_a$) at long $\lambda$
  - Penetrates deeply
- With light cause appropriate biologic effects; it works *in vivo*

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Light Dosimetry

- Light source’s spectral output must match:
  - an absorption peak of the photosensitizer
  - Location of the target at depth

Light Dosimetry

- The wavelength must have sufficient photon energy to initiate a photochemical reaction
### Light Source
- Low power
- Low Irradiance
  - High irradiance may cause
    - rapid tissue oxygen depletion
    - may limit the photodynamic effect
- Continuous or pulsed light sources
  - LED light (continuous)
  - Intense pulsed light/pulsed dye laser

### Mechanism of Action
- Hydrophilic photosensitizer
  - 5-ALA
  - Methyl-ALA
  - Cellular > Vascular

### Clinical Results
- **Complete Response**
  - No clinical and/or histopathological evidence for the treated disease at the site of drug and light application
- **Partial Response**
  - Reduction of ≥ 50% in lesion number or size
- **No Response**
  - Reduction of < 50% reduction

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### Δ5-Aminolevulinic Acid (Levulan)
- Levulan (ALA HCL)
- DUSA Pharmaceuticals  Tarrytown, NY
**Photodynamic Therapy**

**∆5-Aminolevulinic Acid**
- Absorption Spectrum

- Efficient, intracellularly-produced photosensitizer (PpIX)
- Topical applied 20% solution
- Application time
  - 30 mins - 12 hours – Depends on condition treated
- Blue light (417nm) or red light (600-700nm) or IPL/PDL
- Photosensitivity – 36 hours

**International Society of Photodynamic Therapy (2005)**

- Actinic Keratosis
  - Level 1A
- Superficial & nodular basal cell carcinoma
  - Level 1A
- Bowen’s Disease/SCCIS
  - Level 1A
- Acne/sebaceous hyperplasia
- Warts
- Photodamage

**Δ5-Aminolevulinic Acid**

- Actinic Keratosis
  - Piacquadio DJ, et al Arch Derm 2004;140:41-6
  - Largest, multi-center, phase 3 trial (US)
  - 243 pts with > 1700 AKs
  - 91% of **AK lesions** showed complete response at 12 wks vs. 25% controls (p<0.001)
  - 89% of **patients were > 75% clear** vs. 13% controls at 12 weeks (p<0.001)
## Photodynamic Therapy

### Δ5-Aminolevulinic Acid (Levulan)

- 20% ALA x 24 hours, 10J/cm² 417nm

<table>
<thead>
<tr>
<th>Pre-PDT</th>
<th>3 d Post-PDT</th>
<th>6 wks Post-PDT</th>
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![Pre-PDT Image](image1)

![3 d Post-PDT Image](image2)

![6 wks Post-PDT Image](image3)

![Levulan Packaging](image4)
Photodynamic Therapy

5-Aminolevulinic Acid (Levulan)

20% ALA x 24 hours, 10J/cm² 417nm
30 mins to 24 hrs later...

Sun protection measures:
- Clothing
- Total Block
- Sun avoidance (away from windows)
  24-36 hours
Photodynamic Therapy

\[ \Delta 5\text{-Aminolevulinic Acid} \]

AK lesion response in patients treated with ALA PDT

<table>
<thead>
<tr>
<th>Patient 2</th>
<th>24 hours after treatment</th>
<th>1 week after treatment</th>
<th>8 weeks after treatment</th>
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<tr>
<td>Baseline</td>
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Fig. 167: Multiple AK on the cheek. Fig. 168: Therapeutic ALA PDT. Detection of all neoplastic skin areas. Fig. 169: One day after PDT with red light (630 nm). Improvement with ALA. Fig. 164: One month after PDT, facial skin is clear and smooth without any scar or keloids.

Δ5-Aminolevulinic Acid

Fig. 161: Multiple AK on the cheek. Fig. 162: Therapeutic ALA PDT. Detection of all neoplastic skin areas. Fig. 169: One day after PDT with red light (630 nm). Improvement with ALA. Fig. 164: One month after PDT, facial skin is clear and smooth without any scar or keloids.
Photodynamic Therapy. 4 hours levulan, followed by IPL light, 555 nm filter, 20-30 ms pulse duration

Δ5-Aminolevulinic Acid

- Topical ALA-PDT for nodular BCC
  - 149 patients with 173 nBCCs
  - Randomized to ALA-PDT or surgical excision with 3 mm margin
  - Endpoint: histologic clearance
  - At 3 mos:
    - 94% with ALA-PDT
    - 98% surgical excision
    - 3 year interim analysis:
      - 2.3% recurrence rate surgery
      - 30% PDT

- Topical MAL-PDT for nodular BCC
  - Rhodes et al. Arch Derm 2004;140:17-23
  - 101 subjects, biopsy proven and untreated nBCCs
  - Randomized to MAL-PDT, 2 Rxs, 1 week apart or surgical excision with 5 mm margin
  - Endpoint: histologic clearance
  - At 3 mos:
    - 91% with ALA-PDT
    - 98% surgical excision
    - 2 year interim analysis:
      - 5 recurrences in MAL PDT group
      - 1 recurrence excision group
Δ5-Aminolevulinic Acid

Fixing ALA penetration problem:
- Multiple treatment regimens
- Pre treat skin with microdermabrasion/laser or chemical peel
- Topical enhancers: Dimethylsulfoxide (DMSO), desferroxamine (higher PPIX concentration)
- Tissue Preparation
  - Curettage
  - Prolonged ALA application – 48hours
  - Intralesional ALA application

International Society of Photodynamic Therapy (2005)

Actinic Keratosis
- Level 1A

Superficial & nodular basal cell carcinoma
- Level 1A

Bowen’s Disease/SCCIS
- Level 1A

Suppression of NMSCs in the immunosuppressed
- Level 2A

Δ5-Aminolevulinic Acid Indications

- Epithelial hyperproliferations and neoplasias
  - AKs
  - BCC superficial and nodular
  - SCC in situ
  - Aks
  - Verruca and condyloma
  - Psoriasis
- Photodamage
  - Photodamage
  - With IPL
- Acne/sebaceous hyperplasia/hidradenitis
- Vitiligo
- Hirsutism
  - Terminal white hairs – topical aminolevulinic acid plus combined radiofrequency and optical light treatment
- Cutaneous Malignancy
  - CTCL
Photodynamic Therapy

5-Aminolevulinic Acid

**Treatment Protocol**
- **Degrease skin**
- +/- microdermabrasion or erbium laser peel
- **Apply 5-ALA**
  - 10-20 mins – pore size
  - Half an hour – acne
  - 1-2 hours – photodamage/actinic keratoses
  - 14-18 hours – actinic keratoses/superficial cancer
- **Blue or red light**
  - Blue light 16 min:40 seconds (10 j/cm²)
  - Red light 20 mins (75-150 j/cm²)
  - IPL – low fluence
- **Activate with red light** --better for acne because of deeper penetration
- **Frequency varies with endpoint**

Sunblock SPF 30
- Stop retinoids till skin re-epithelialized
- Avoid outdoor activity for at least 48 hours
- Cold compresses
- Bland emollients
- Bio-restorative ointments
- Hydrocortisone gel 1%/aloe vera gel
- **Safety in dark skin patients debated**
  - Only 1 case report in African American
  - Multiple reports in Asian population
  - Reports of post-inflammatory pigmentation but not scarring
  - Only 1 study in African American patient
**Blue Light**

- 417 nm
- 10mW/cm²
- Lamp lifetime ~ 100’s hours
- Cost ~ Lease (q month)
- DUSA Tarrytown, NY
- 16 mins:40 sec

**Other PDT Light Sources**

- Red Light LED
- IPL

**Methyl-esterified ALA**

- Metvixia
- Available since 2009 for use in photodynamic therapy
- Galderma (Fort Worth, TX)
- Photocure (Oslo, Norway)
- FDA approved for nonhyperkeratotic AKs
- Enhanced lipophilicity enables deeper penetration
- Often activated with RED light (Aktilite) and IPL, given its greater depth of penetration
- Increased efficacy for acne?

**PDT – Advantages**

- Rapid treatment of multiple or large areas
- Covered by Medicare/insurance for AKs
  - CPT 96567, 37308 (aminolevulanic acid)
  - Covered for ICD-9 702.0 (AK)
- For acne, varies with insurance. Obtain precertification
- Non-invasive
- Generally good cosmetic results
  - Cosmetic “appetizer”
  - Relative few side effects
  - No cumulative toxicity
- Capability for diagnosis
  - Photodynamic diagnosis
Photodynamic Therapy

**PDT: Disadvantages**

- Generalized photosensitivity with systemic administration
- UVA/B chemical sunscreen ineffective
- Adverse Effects – Local pain, redness, erythema
- Time – from drug delivery to end of irradiation
- Poor insurance/Medicare reimbursement versus other destructive modalities

**References**


