

Photodynamic Therapy

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Conflict of Interest Disclosure

Dr. Gilchrest serves as a consultant to DUSA Pharmaceuticals, manufacturer of Levulan Kerasticks® and the Blu-U Therapeutic Illuminator®. Her department has received Kerasticks and Blu-U light source to support clinical studies.

Photodynamic Therapy

Definition

Light activation of photosensitizer to generate highly reactive oxygen intermediates => *tissue injury and necrosis*

FDA-approved photosensitizers:

Porfimer sodium (photofrin II)

IV, activity lasts for weeks

Visudyne (verteporfin)

IV, activity lasts 3 days

Aminolevulinic acid (ALA)

Topical, activity lasts ~ 2 days

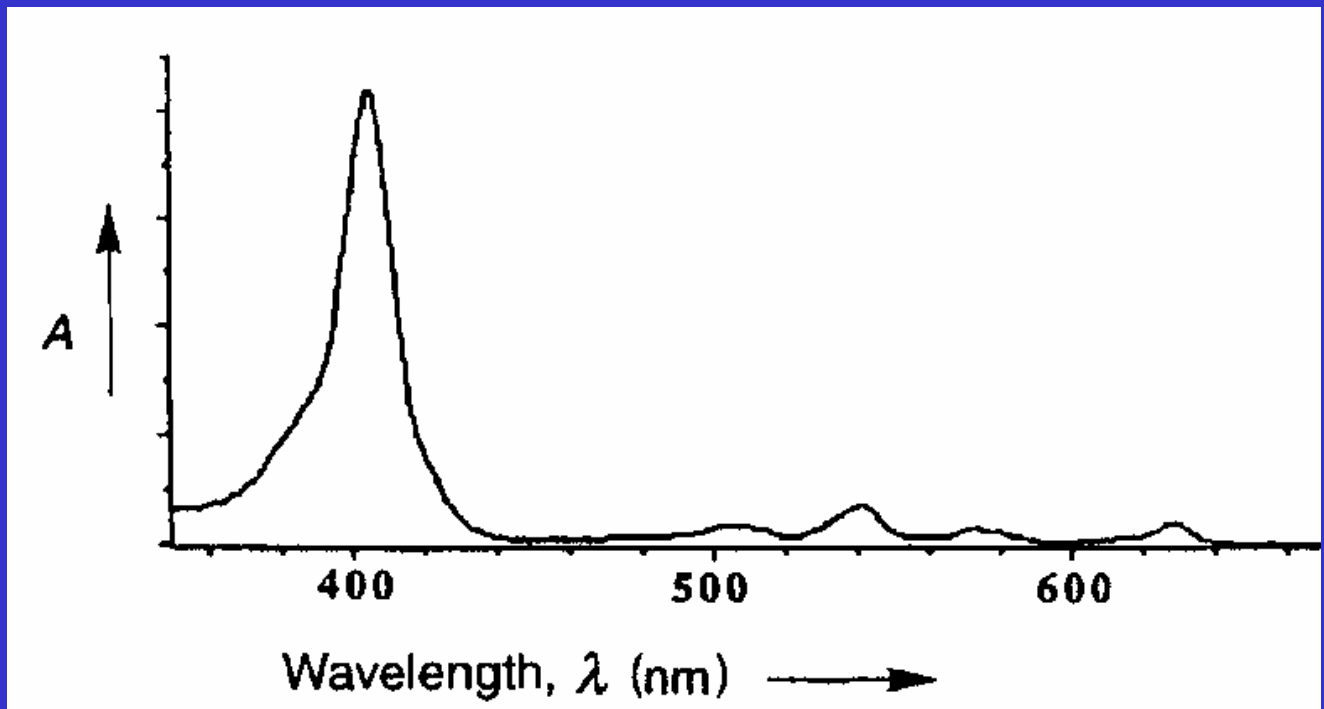
Prodrug, metabolized to protoporphyrin IX

Available Topical Photosensitizers for Photodynamic Therapy

Compound	Aminolevulinic acid (ALA)	Methyl aminolevulinate (MAL)
Final active metabolite	Photoporphyrin IX	Protoporphyrin IX
Preparation	Solution	Peanut Oil Based Cream
Brand name	Levulan (DUSA Pharmaceuticals)	Metvix (Galderma)
Approval in	USA	Europe, Australia, New Zealand, (USA)
Approved for	AKs only	AKs, Bowen's disease, sBCCs, nBCCs
Co-approved light source	Blue light	Red light

Absorption (Activation) Spectrum for Porphyrins

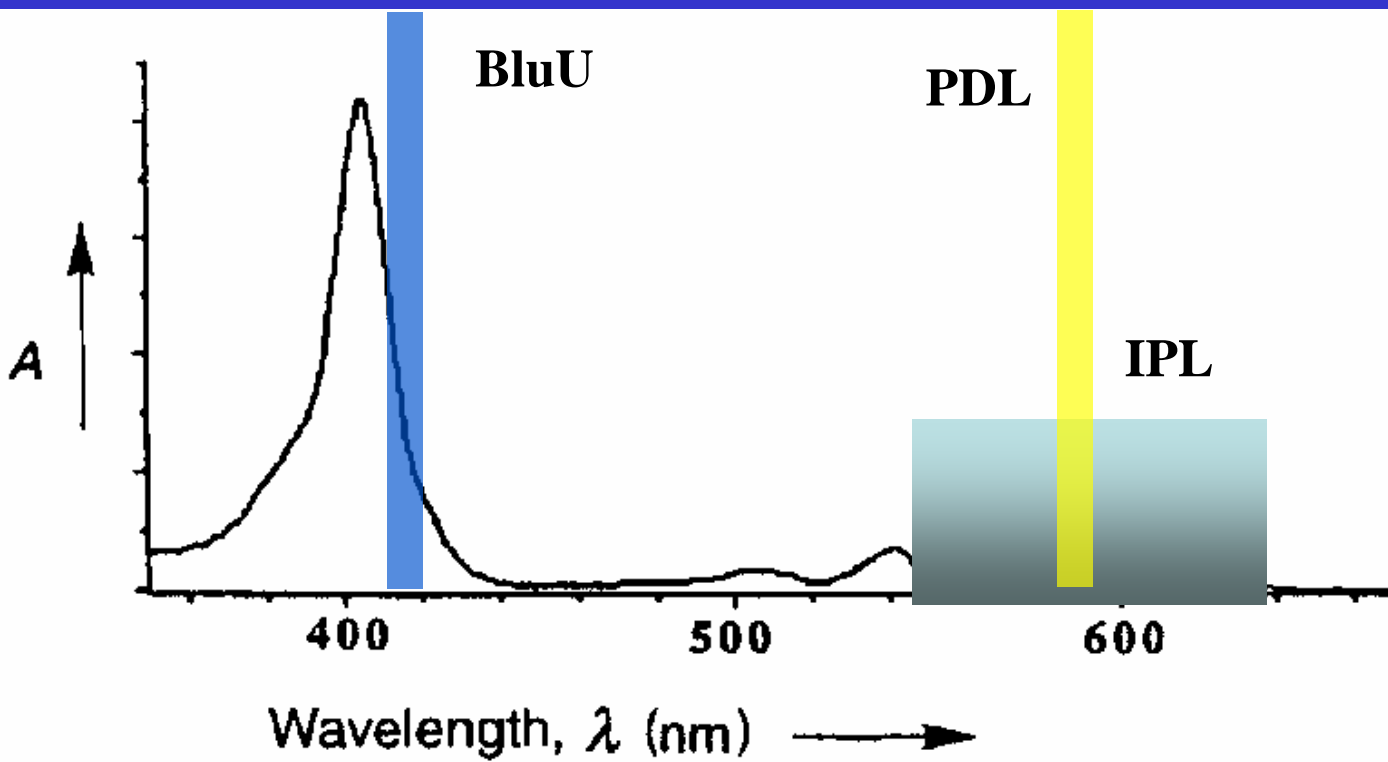
Soret Band



Conclusion: Blue light activates porphyrins most efficiently

Absorption (Activation) Spectrum for Porphyrins

Soret Band



Increased PDT Effect in AKs or SCC vs Normal Skin

- Increased ALA penetration (abnormal stratum corneum)
- ALA always metabolized principally to protoporphyrin IX
- Lower intracellular $[Fe^+]$ and hence porphyrins less converted to heme

Heme Biosynthesis Pathway

ALA



Porphobilinogen



Multiple Intermediates

(Porphyrinogens, Porphyrins)



Protoporphyrin



Fe^H

Heme

FDA-Approved ALA-PDT

- **Focal treatment of AKs**
- **14-18 hour incubation**
- **Blue light (417 nm) exposure
(10J/cm²)**
- **Pivotal trial results**
 - **75-90% of treated AKs
resolved at 1 month**
 - **Rates comparable to LN₂
and approved field
therapies**
 - **No scarring**

BU Versus FDA-Approved Protocol for AKs

- **Treatment area:**
Entire face vs. AKs only
- **ALA incubation period:**
1-3 vs. 18 hours

Rationale for modifications

- **Entire face is photodamaged**
- **Optimum skin cancer prevention**
- **Short ALA incubation is
convenient and adequately
photosensitizing**
- **Patient motivation**

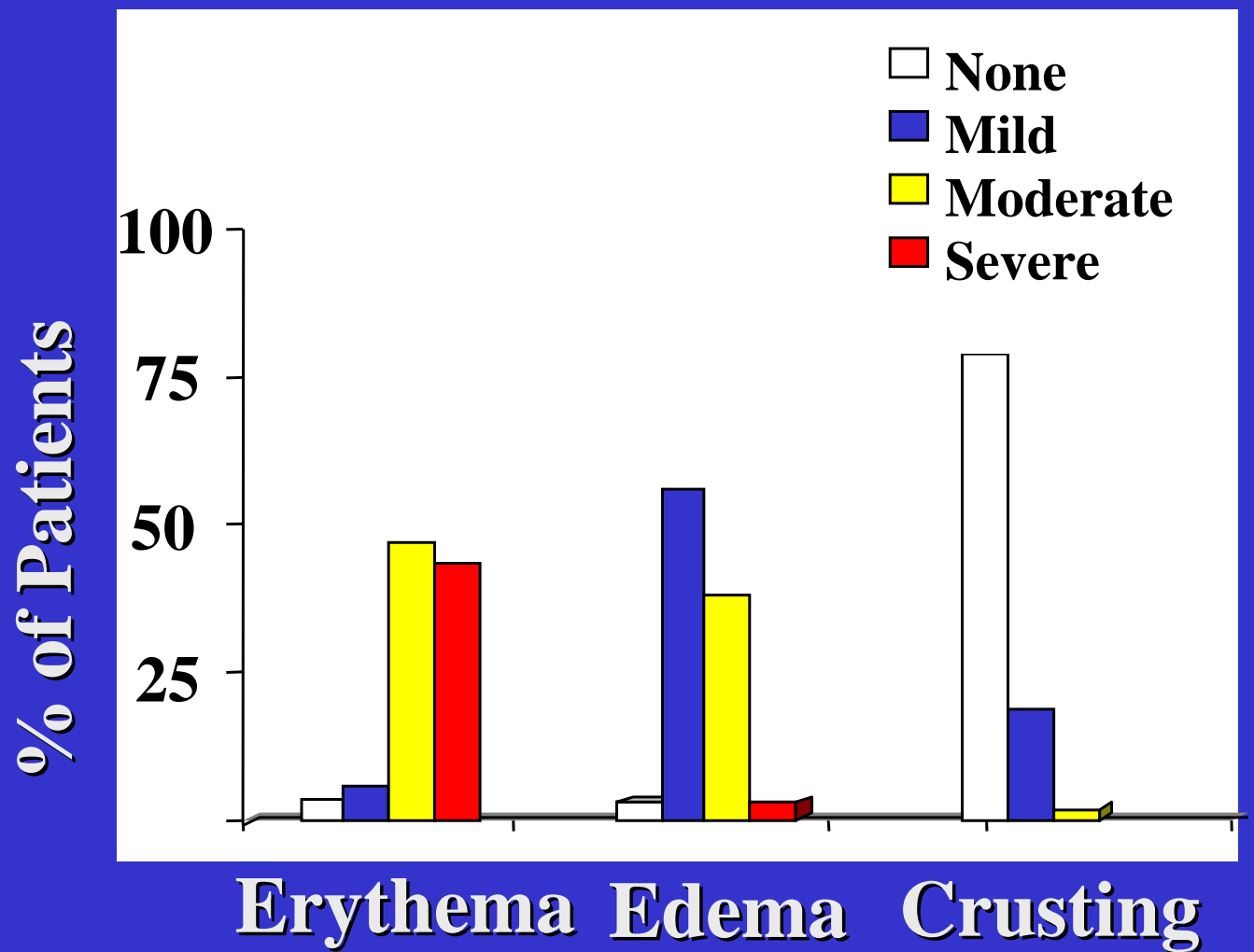
ALA-PDT: During Treatment



**DUSA Blu U Lamp
Kerasticks®: 20% ALA**

Phototoxicity After ALA-PDT

Peak: Day 1



Severity of ALA-PDT Photosensitization



Touma et al. Arch Dermatol, 2004

Unusual Idiopathic Pustular Eruption Following ALA-PDT



Improvement in Signs of Photodamage After ALA-PDT



Touma et al. Arch Dermatol, 2004

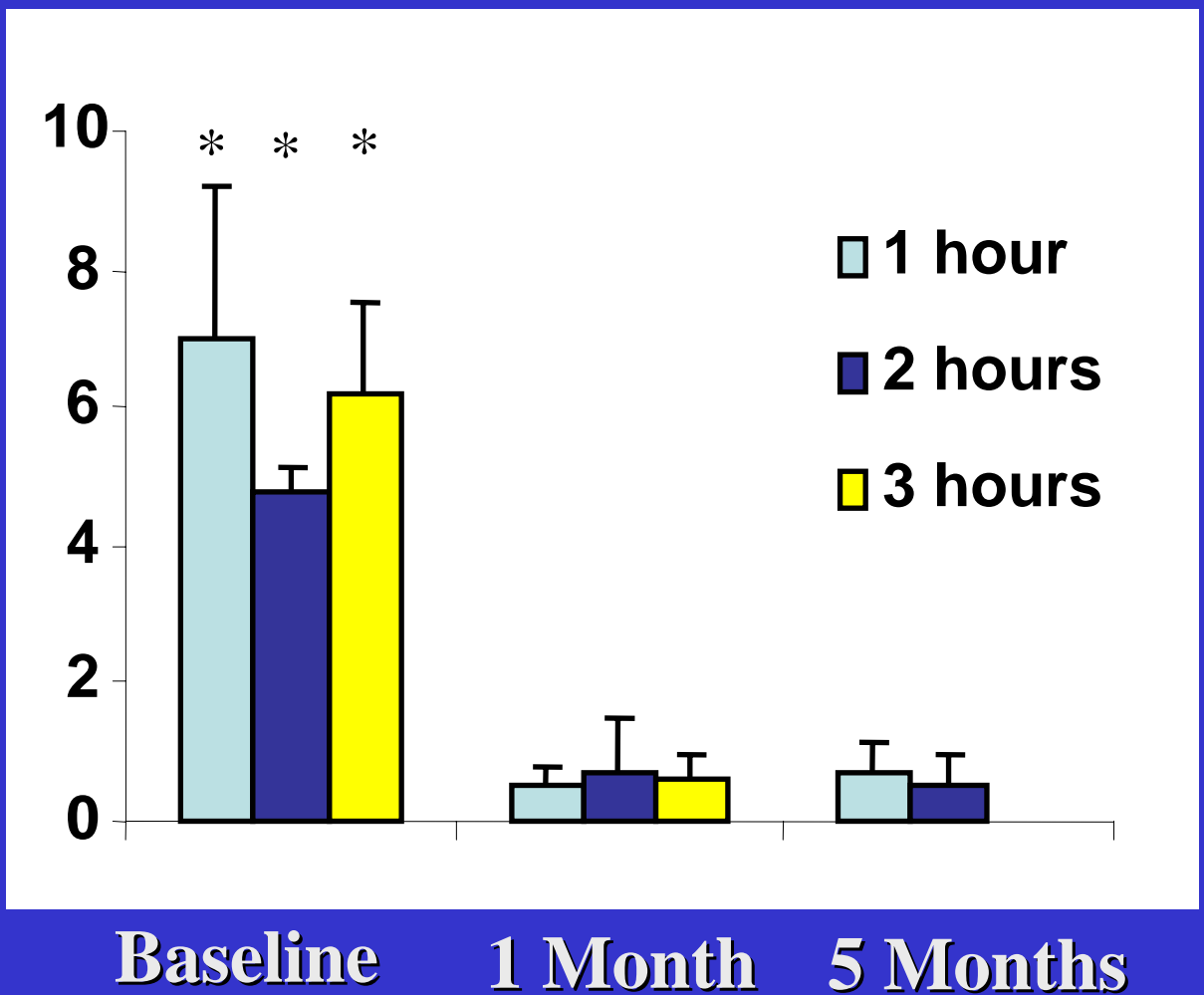
Improvement in AKs and Erythema After ALA-PDT



Touma et al. Arch Dermatol, 2004

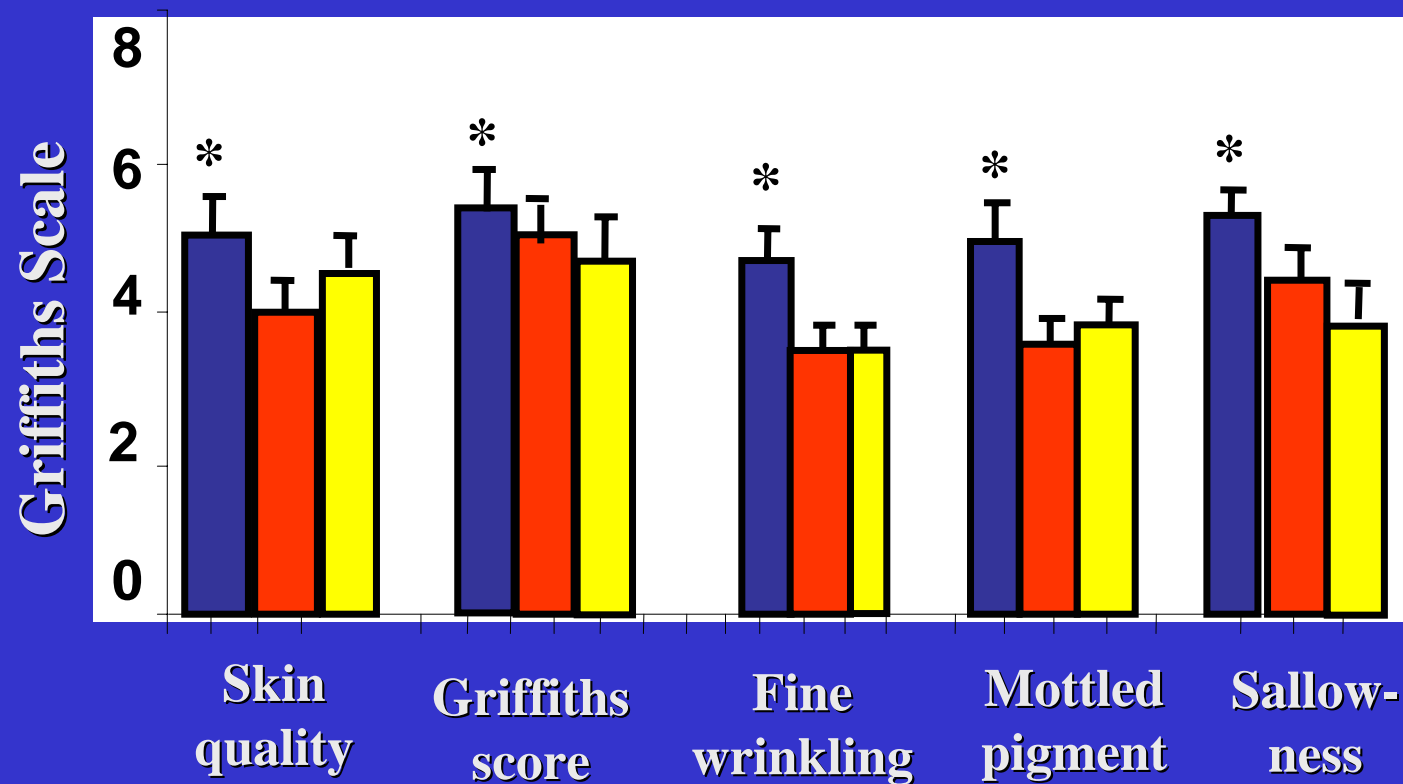
Improvement in AKs After ALA-PDT

Average Number of AKs



* $p < 0.001$ Pre vs. Post-Rx

Improvement in Photoaging Signs After ALA-PDT



* $p < 0.01$ to $p = 0.05$
Pre vs. Post-Rx

■ Baseline
■ One month
■ 5 months

Conclusions

Short Incubation

Broad Area ALA-PDT

- **As safe and effective for AKs as the FDA-approved protocol**
- **One session is more effective for photoaging than 6 months of daily retinoic acid applications, comparable to a TCA peel**
- **Likely to reduce risk of skin cancers**
- **Optimum regimen still unknown**
- **Patient satisfaction very high**

Guidelines for Use of PDT (2005)

International Society for PDT in Dermatology

(Braathen et al. JAAD, 2007)

- **Based on MEDLINE search, primarily European experience, 5 year follow-up, considering safety, efficacy, cosmesis and patient preference**
- **Premalignant and malignant indications only**
- **Recommendations A-E and I-IV**
A1: Good evidence in support based on at least one well designed randomized controlled trial

Guidelines for Use of PDT (2005)

International Society for PDT in Dermatology

Treatment

- AKs – focal or broad area (11 studies) **AI**
- Bowen's disease (4 studies) **AI**
- SCC (3 open label studies) **C II iii**
- s BCC (12 studies) **AI**
- n BCC (12 studies) **AI**

Prevention

(in organ transplant patients)

- AKs **BI**
- SCC **C III**
- BCC **C II iii**

International Society for PDT Conference Recommendations for Topical PDT

AKs: Highly effective, excellent
cosmesis, first line therapy

Bowen's disease: As for AKs

SCC: Insufficient evidence to support
routine use

sBCC: Effective and reliable (5 yr f/u),
excellent cosmesis, especially
good for large and/or multiple
lesions

nBCC: For lesions < 2mm deep, as above

Prevention (immunosuppressed patients):

AKs - Good evidence

SCC and BCC – Weak evidence

Boston Experience with NMSC High Risk Groups

- Organ transplant recipients
SCCs in 7% after 1 year and in 70% after 20 years¹
10X↑ risk of BCC²
40-150X↑ risk of SCC²
- Gorlin syndrome patients
Up to hundreds of BCCs
- Patients with a prior NMSCs
NMSC in >1/3rd within 1 year^{3,4}

¹ Bouwes et al. Transplantation, 1996
(figures for Australia)

² Lindelof et al. Br J Dermatol, 2000

³ Schreiber et al. JAAD, 1990

⁴ Frankel et al. JAAD, 1992

ALA Photodynamic Therapy for Basal Cell Nevus Syndrome

E.B. 22 years old



**Before
Treatment**

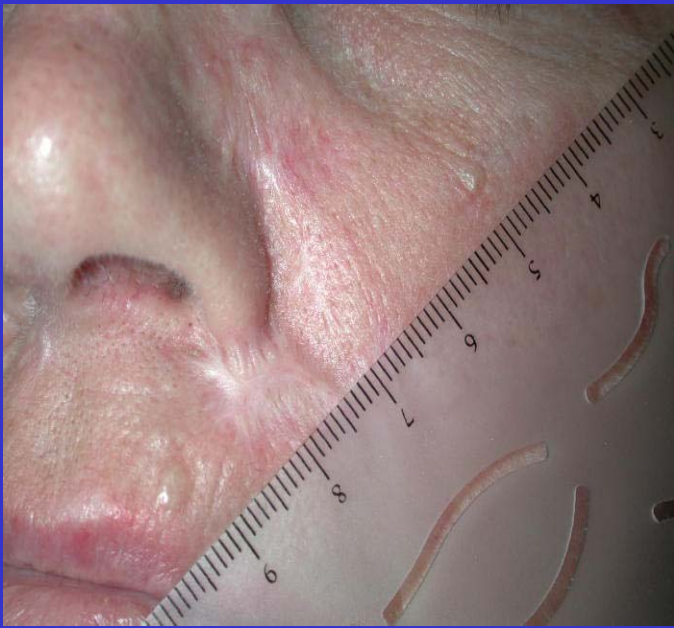


**Six months after
Treatment 3**

No recurrence after 7 years

ALA Photodynamic Therapy for Basal Cell Nevus Syndrome

C.C. 46 years old

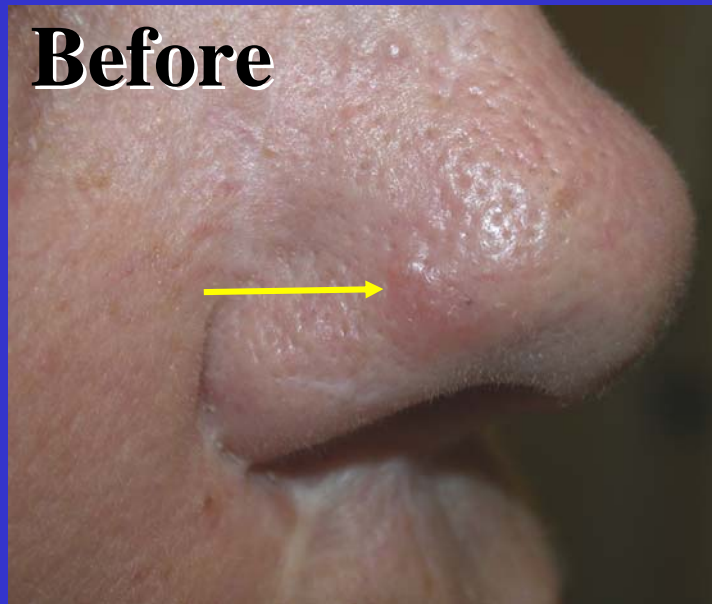


**Before
Treatment**



**After
4 Treatments**

Classic BCC in BCNS Patient, Resolved After One ALA-PDT Session



No recurrence after 2 years

Broad Area PDT in BCNS

G.S. 67 years old



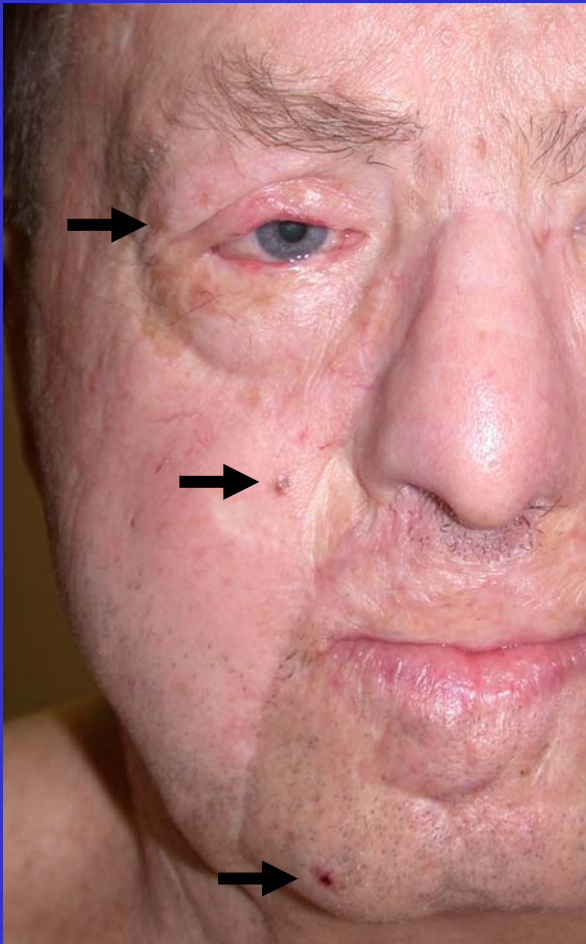
Pretreatment



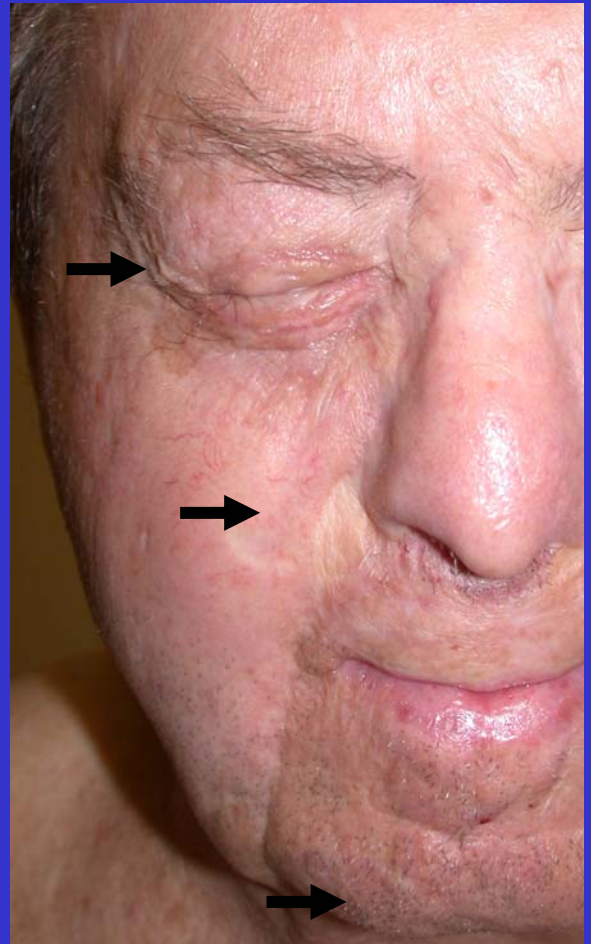
**After
3 Treatments**

Broad Area PDT in BCNS

G.S. 70 years old



Pre-Treatment



Post-Treatment

3 new BCC after a 1 year hiatus in prophylactic PDT sessions

Intralesional Treatment of Nodular BCC in a Patient with BCNS



Pretreatment



1 month

BluU lamp (417 nm) 10 J/cm²

ALA 20% diluted 1:1 in 1% epinephrine

Intralesional Treatment of Nodular BCC in a Patient with BCNS



Pretreatment



2 months

BluU lamp (417 nm) 10 J/cm²

ALA 20% diluted 1:1 in 1% epinephrine

Oseroff et al. Treatment of diffuse basal cell carcinomas and basaloid follicular hamartomas in NBCCS by wide-area ALA-PDT. Arch Dermatol 141: 60-67, 2005

Patients:

- 6, 10 and 17 y.o at presentation
- 2 S/P XRT for medulloblastoma
- 12-25% BSA involved with BCC or BFH

Treatment:

- ALA 2.5-20% in cream base applied overnight
- Red light from laser (633 nm) or tungsten-hologen lamp (590-700 nm)
- Each session 3-6 hours under general anesthesia

Treatment Outcomes (Oseroff et al)

- BCC/BFH resolution rate 85, 90, and >98% in 3 patients after 4-7 sessions
- No new lesions in treated areas after 1.8 – 6 yr follow up from last session
- Radiation dermatitis cleared (one patient)
- Moderate erythema and mild edema, peaking 24-36 hr post-treatment, well tolerated

5 Year Randomized Prospective Trial of MAL-PDT vs Surgery for Nodular BCCs

Rhodes et al. Arch Dermatol, 2007

- 97 Patients (105 BCCs)
- MAL-PDT 2 (77%) or 4 (23%) times/BCC
- Recurrences after 5 years: 14% of MAL-PDT treated vs 4% of excised BCCs (P=0.09)
- Good to excellent cosmetic outcomes

	3 Months	5 Years
MAL-PDT	82%	87%
Surgery	33%	54%

$p < 0.007$ MAL-PDT superior

Renal Transplant Recipient

**37 years post transplant,
dozens of SCC**



Before Treatment



**1 month s/p first
ALA-PDT session**

Erythroplasia of Queyrat

75 y.o., scheduled for surgical excision



Before

**10 months s/p 3 ALA-PDT sessions –
scouting biopsies
negative**

Chronic Radiation Dermatitis

65 y.o., many X-ray exposures
as a child, biopsy-proven SCC.



Before



**1 month s/p 2
ALA-PDT sessions**

No recurrence after 3 years

Conclusions

- Intermittent broad area ALA-PDT can greatly reduce BCC incidence in BCNS patients
- Topical or intralesional Levulan®/Blu U® ALA-PDT eradicates many BCCs without scarring
- ALA-PDT can improve the appearance of scarred photodamaged skin

Advantages of ALA-PDT in these settings

- **Excellent patient tolerance**
- **No scarring**
- **Cosmetic improvement**
- **Decreased risk of new malignancies**
- **Low cost compared to alternatives**