Update on Daylight-PDT Practice in Medical and Cosmetic Clinic

Rolf-Markus Szeimies
Recklinghausen, Germany
DISCLOSURE OF RELATIONSHIPS WITH INDUSTRY

Rolf-Markus Szeimies, MD PhD
F024 Photodynamic Therapy in Medical and Aesthetic Dermatology

DISCLOSURES

Almirall, Biofrontera, Galderma, LEO Pharma: Advisory Board – Honoraria
Almirall, Biofrontera, Galderma, Janssen Pharmaceuticals: Speaker – Honoraria
Biofrontera, Galderma, LEO Pharma, photonamic: Investigator – Grants
FURTHER DISCLOSURE

Rolf-Markus Szeimies, MD PhD
F024 Photodynamic Therapy in Medical and Aesthetic Dermatology

All drugs and procedures/combinations presented here in this talk are not approved in the U.S. by the FDA
Mechanism of pain induction by classical PDT

Ang JM et al. (2017) Photodiagnosis Photodyn Ther 19:308-344
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Mechanism of pain induction by classical PDT

Ang JM et al. (2017) Photodiagnosis Photodynm Ther 19:308-344

Illumination with red light

after 180 min
PDT

• Painless
• Daylight
• Therapy

Prof. H.C. Wulf, Copenhagen Bispebjerg University Hospital
Daylight-PDT for Actinic Keratoses

Wiegell S et al., Br J Dermatol 2008; 158: 740-6

PDT for AK is painful, especially in field cancerized areas of face & scalp

Better tolerability, when light at lower intensity is used for illumination?

Comparison of conventional MAL-PDT (3 h incubation, LED 37 J/cm²) vs. daylight exposure (30 min MAL incubation followed by 2.5 h sun exposure)
Daylight-PDT: significantly reduced pain at equal efficacy

<table>
<thead>
<tr>
<th>First study with 29 patients</th>
<th>Wiegell, BJD 2008</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Conventional PDT</td>
</tr>
<tr>
<td>AK severity (following Olsen grading)</td>
<td>66% grade I 33% grade II</td>
</tr>
<tr>
<td>Average daylight exposure (min)</td>
<td>--</td>
</tr>
<tr>
<td>Complete lesion response rate of grade I AK</td>
<td>71%</td>
</tr>
<tr>
<td>Average maximum pain score</td>
<td>6.7</td>
</tr>
</tbody>
</table>
Daylight-PDT for Actinic Keratoses

Wiegell S et al., Br J Dermatol 2008; 158: 740-6

VAS Pain Score lower on daylight-side

Image from original publication
Decreased pain with simultaneous synthesis of PPIX and daylight illumination

Ang JM et al. (2017) Photodiagnosis Photodyn Ther 19:308-344
Decreased pain with simultaneous synthesis of PPIX and daylight illumination

Ang JM et al. (2017) Photodiagnosis Photodynl Ther 19:308-344
<table>
<thead>
<tr>
<th>Objective</th>
<th>Wiegell et al.\textsuperscript{12}</th>
<th>Rubel et al.\textsuperscript{19}</th>
<th>Lacour et al.\textsuperscript{20}</th>
</tr>
</thead>
<tbody>
<tr>
<td>To compare conventional PDT to red light PDT to daylight PDT (response rates and adverse effects)</td>
<td></td>
<td>To evaluate the noninferiority of daylight PDT vs conventional PDT and intensity of pain caused</td>
<td>To demonstrate the noninferiority of efficacy and the superiority of safety of daylight PDT vs conventional PDT</td>
</tr>
<tr>
<td>Trial design</td>
<td>Randomized, controlled, single blind</td>
<td>Phase III trial, multicenter, randomized, controlled, single blind</td>
<td>Phase III trial, multicenter, randomized, controlled, single blind</td>
</tr>
<tr>
<td>Country</td>
<td>Denmark</td>
<td>Australia</td>
<td>France, Germany, Spain, Switzerland, the Netherlands</td>
</tr>
<tr>
<td>No. of centers</td>
<td>1</td>
<td>7</td>
<td>18</td>
</tr>
<tr>
<td>Analytic approach</td>
<td>NS</td>
<td>PP, ITT of efficacy</td>
<td>PP, ITT of efficacy</td>
</tr>
<tr>
<td>Follow-up, wk</td>
<td>12</td>
<td>24</td>
<td>12</td>
</tr>
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</table>
MAL-Daylight PDT in AUS & Europe – Phase-III-Studies

Split-face design
AK patients
(facial/scalp AK, mild/moderate lesions; Olsen I+II)

Daylight PDT

Application of chemical sunscreen → Pre-treatment of skin → Application of MAL → Daylight exposure for 2 h → Removal of MAL

Red light PDT

Pre-treatment of skin → Application of MAL → Occlusion for 3 h → Removal of MAL → Illumination with red light

versus

Lacour JP et al. JEADV 2015;29:2342-8
Noninferiority of DL-PDT to cPDT in AK


**Figure 3**  Forest plot comparing response rates for conventional versus daylight PDT according to intention-to-treat analysis. The figure shows that the CIs were below the noninferiority margins established a priori (20% by Rubel et al.\textsuperscript{19} and 15% by Lacour et al.\textsuperscript{20}). Thus, daylight PDT can be considered noninferior. PDT refers to photodynamic therapy and diff. to difference.
Almost no pain with daylight-PDT in the pivotal trials

Visual analogue scale following light exposure (0-10)

- MAL daylight PDT
- MAL red light PDT

Australia: 0.8 (p<0.001) vs. 5.7
Europe: 0.7 (p<0.001) vs. 4.4
Natural Daylight PDT – “Recklinghausen Style”

• Chemical sunscreen SPF50+ 15 min before...
• Lesion preparation (in case of crusty AKs)
• Application of photosensitizer
  • thin layer
  • no occlusion
• start of light exposure within 30 min
• light exposure outside for 2 h
  • minimum LUX: 2,300; period between Apr-Oct (latitude-dependent)
  • minimum temperature: 10°C / 50°F
Investigator initiated studies have confirmed the efficacy of DL-PDT for the treatment of AK

<table>
<thead>
<tr>
<th>Studies</th>
<th>AK Type (Olsen Grade)</th>
<th>Lesion response rate with MAL DL-PDT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fai D et al (2014)</td>
<td>I &amp; II</td>
<td>82.6 %</td>
</tr>
<tr>
<td>Torezan L et al (2015)</td>
<td>I &amp; II</td>
<td>86 %</td>
</tr>
<tr>
<td>Sotiriou E et al (2015)</td>
<td>I &amp; II</td>
<td>77.9 %</td>
</tr>
<tr>
<td>Cantisani C et al (2015)</td>
<td>N/A</td>
<td>95 %</td>
</tr>
</tbody>
</table>

Case series with 80 pat.
- multiple Aks located at face, chest, arms, legs
  - slight curettage prior to photosensitizer application
- chemical sunscreen 30 min prior to ALA
- ALA 1h prior to light exposure
Subsequent daylight exposure outside in the shade for 2.5h
chemical sunscreen on following day and subsequent exposure to shaded or direct sunlight for 15-30 min
Achievement of obvious improvement in photodamage
Significantly less pain than with c-PDT
## Daylight-PDT – Recent Developments

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Autor(s)</th>
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<tr>
<td>DL-PDT also works with white light for AK</td>
<td>O’Gorman SM et al. (2016) JAMA Dermatol</td>
</tr>
<tr>
<td>Pretreatment with 5-FU enhances efficacy in DL-PDT of AK</td>
<td>Nissen CV et al. (2017) Acta Derm Venereol</td>
</tr>
<tr>
<td>Pretreatment with calcipotriol improves DL-PDT efficacy in AK</td>
<td>Galimberti GN (2017) Photodiagnosis Photodyn Ther</td>
</tr>
<tr>
<td>High patient satisfaction with DL-PDT</td>
<td>Fargnoli MC et al. (2017) JEADV; See JA et al. (2017) Dermatol Ther</td>
</tr>
<tr>
<td>DL-PDT for face &amp; scalp cancer prevention</td>
<td>Sotiriou E et al. (2017) JEADV</td>
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Daylight-PDT suitable for BCC?


- Open, uncontrolled study in 21 pat. with 32 BCCs (all sites)
- 2 tx one week apart; sunscreen, followed by MAL and consecutive daylight exposure for 150 min
- At 3mo follow-up, CR in 30 lesions (94%), 19 pat. (90%)
- At 12mo follow-up, 21% RR (6/29), still 74% CR (23/31)
Optimizing DL-PDT outcome by physical pretreatments (fractionated CO₂-laser, microneedling, sandpaper abrasion)

Philipp-Dormston W et al.: Daylight photodynamic therapy with MAL cream for large scale photodamaged skin based on the concept of ‘actinic field damage’: recommendations of an international expert group. JEADV 2016 30:8-15
Finally, caveats

Be careful with therapeutic protocols which do not adhere to the recommendations in case AKs or BCCs are in the target area

- Lower photosensitizer concentrations
- Shorter incubation times
- Other light sources & fluences