PHOTOSENSITIZERS AND LIGHT SOURCES FOR PHOTODYNAMIC THERAPY OF ACTINIC KERATOSIS

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Abstract. *Actinic keratosis are the most common premalignant skin tumors. Current modalities of treatment include surgical methods (cryosurgery, curettage, electrosurgery, laser surgery) and non-surgical methods (topical chemotherapy, dermabrasion). Over the past few years, the photodynamic therapy has been shown as an useful method for the treatment of actinic keratosis. Photodynamic therapy consists in administration of a photosensitizer which may be preferentially localized in tumors and its subsequent activation by light at an appropriate wavelength. The induced photochemical effect results in the irreversible destruction of the target tissue. This paper will focus on the approved and experimental photosensitizers and light sources for photodynamic therapy and discuss their potential benefits for treatment of actinic keratosis.*

Introduction

Actinic keratosis (AK) is a UV light-induced lesion of the skin that may progress to invasive squamous cell carcinoma. It is by far the most common lesion with malignant potential to arise on the skin. AK is seen in fair-skinned persons in areas of long-term sun exposure. Although the premalignant nature of AK was recognized almost 100 years ago, the name AK was not introduced until 1958. The name literally means thickened scaly growth (keratosis) caused by sunlight (actinic). These lesions can be treated by cryosurgery, curettage, electrosurgery, laser surgery, topical chemotherapy and dermabrasion. In recent years photodynamic therapy has been shown as useful for the treatment of this disease.

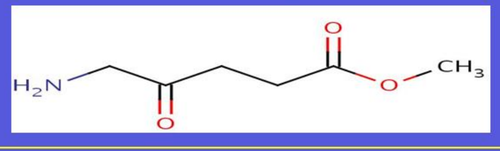
Photodynamic therapy is based on photooxidation of living matter implicating three basic constituents: the photosensitizing substance, the radiation (with a wavelength appropriate to the maximum absorption of the substance in use), and oxygen. Oxygen species, in different toxic forms, constitute the most important agents in the processes of cellular death during the photodynamic therapy.

Photosensitizing substances used in photodynamic therapy of Actinic Keratosis

The most common photosensitizers used for the photodynamic treatment of actinic keratosis are:

- 5 - aminolevulinic acid (5-ALA)

- methyl - 5 aminolevulinat (MAL)



Light sources

For photodynamic therapy of Actinic Keratosis we use :

- coherent sources:
  - Pulsed dye lasers (PDL) (585 nm and 595 nm)
- non-coherent sources:
  - Lamps:
    - Blue fluorescent light
    - Filter-modificated slide projector
    - Intense pulsed light devices (IPL)
  - LEDs

Results

1. ALA - PDT of Actinic Keratosis

PS	Type of laser	Parameters	Observations	References
ALA c = (10 - 30)%	Blue, violet, green, red light sources	1-2 sessions incubation: time (3 -6) h	1 sesion - rate of cure: (71 - 100)% the light sources have shown the equql effectiveness	Poljacki M et.al. 2006
ALA c = 20%	Light source: Blu-U device	1-2 sessions	at 1 month after one sesion, the rate of cure was 76 %.	Tschen EH et al. 2006
ALA	Short arc plasma discharge sourse	incubation time: 4 h 1-2 sessions light source: P = 300 W; DE = 94-156 J/cm^2	All lesions were cleared after 1 or 2 sessions. During the treatment the pain was absent or mild	Morton Ca et al. 2005
ALA c = 20%	Flash lamp stimulated noncoherent light - filtered from 555 nm to 950 nm	2 sessions $\lambda \in$ (555 - 950) nm τ_{pulse} = 20-30 ms DE = 12 - 16 J/cm^2	50% of lesions were resolved after 1 sessions and 16% of lesions showed residual atypical cells	Hyung Su Kim et al. 2005
ALA c = 20%	Light source: Blu-U device. Nonlaser fluorescent blue light	incubation time: 14-18 h DE = 10 J/cm^2 Power:10mW/ cm^2 Exposure time: 1000 s	At 8 week after treatment, the complete response was 77% and after 12 week folloeing the treatment, the complete response rates was 89% Erytheme, burning and edema were present at many patients	Piacquadio DJ et al. 2004
ALA	intense pulsed light devices (IPL)	1 session incubation time: 1h DE = 28 - 32 10 J/cm^2 τ = 10 ms	At 3 months after treatment, 68% of lesions had resolved	Avram DK et al. 2004
ALA	pulsed dye lasers (PDL)	1 session incubation time: (14-18) h DE = 4.0 - 7.5 J/cm^2 τ = 10 ms	Clearance rates of lesions, at 8 mouth following a single treatment was 90% comparable to traditional treatment	Alexiades-Armenakas Mr et al. 2003
ALA	incoherent red light source	λ = 640 nm 105 J/cm^2	At 12 months the complete response rates was 72%	Varma et al. 2001
ALA	incoherent light source emitting violet light	$\lambda \in$(400 - 450) nm DE = 10-20 J/cm^2	Complete remission in one of the four lesions	Dijkstra et al. 2001
ALA	long-pulse (1.5 ms) tunable flashlamp-pumped pulsed dye laser (LPDL) incoherent light source	λ = 585 nm, DE = 18J/cm^2 DE = 60-160 J/cm^2	79% complete remission with LPDL 84% with incoherent lamp. Pain during light treatment was significantly reduced by using the LPDL.	Karrer et al. 1999

2. MAL - PDT of Actinic Keratosis

PS	Type of laser	Parameters	Observations	References
MAL	light-emitting diode (LED) variable pulsed light (VPL)	DP = 50 mW/cm^2 DE = 37 J/cm^2 DE = 80 J/cm^2, double pulsed at DE = 40 J/cm^2, $\lambda \in$ (610 - 950) nm filtered hand piece	VPL efficient alternative equivalent to LED, but causes significantly less pain	Babilas et al. 2007
MAL	Red light source	1 -2 sessions λ = 634 nm	The cure rate after 12 weeks was 86,9%. The unresolved lesions were re-treated.	Morton C et al. 2006
MAL	LED	λ = 634 nm, DE = 37 J/cm^2 -single treatment - two treatments one week appart	Single treatment effective for thin actinic keratosis lesions; repeated treatment recommended for thicker or non-responding lesions	Tarstedt et al 2005
MAL	Noncoherent red light source	1 session incubation time: 3h DE = 75J/cm^2	69% of actinic keratosis lesions had a complet response after 3 month following treatment; 43% of patients have reported local reactions (itching, burning)	Szeimies RM et al. 2002

Conclusions

- The most common photosensitizers used for photodynamic therapy of actinic keratosis are 5-aminolevulinic acid (ALA) and methyl-5-aminolevulinat (MAL)
- MAL-PDT is already approved in Europe, Australia and New Zeeland and in USA in combination with red light
- ALA-PDT is approved in USA using blue light for irradiation
- There is no difference regarding the profile of light necessary for a successful ALA-PDT or MAL-PDT and both coherent and noncoherent light sources can be used