New protocols in photodynamic laser therapy of tumors (PDT)

Dr. Michael Weber, Institute of Lasertherapy, Lauenförde, Germany
Photodynamic therapy: new ways of cancer treatment with lasers and photosensitizers
The Effects of Intravascular Low Level Laser Therapy in the Scope of a Redifferentiation Therapy of Malignant Tumours

Intravascular laser blood irradiation and the bioimmunotherapy according to Tallberg appear to have additive and synergistic effects in the redifferentiation of tumour cells. The bioimmunotherapy exerts effects on tumour cell mitochondria. By means of mitochondria-nuclear communication malignantly transformed cells can regain their normal gene expression. Intravascular laser blood irradiation changes mitochondria morphologically and activates metabolic energy processes. In an application study these two methods were compared with each other both individually and in combination in maximally chemotherapeutically pre-treated tumour patients. Clinically and morphologically synergistic and additive effects were observed.
Laser blood irradiation in biological cancer therapy in combination with bioimmune therapy (Tallberg, Helsinki)

Group 3: Combination therapy

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<th>Type of tumour</th>
<th>TZ</th>
<th>LSM1</th>
<th>LSM2</th>
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<th>LSM4</th>
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<th>TU marker</th>
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<td>4</td>
<td>4</td>
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Recent research has displayed that high doses of low-level laser therapy (LLT) may encourage the growth of melanoma skin cancer.

High irradiances of low-level laser therapy (LLT) should not be used over melanomas. Researchers writing in the open access journal *BMC Cancer* studied in the pain-relieving, anti-inflammatory cold laser, finding that it causes tumor growth in a mouse model of skin cancer.

Jan M. Bjordal from Bergen University College, Norway,
Introduction: Process of Photodynamic Therapy (PDT)

- 2 individually non-toxic components brought together to cause harmful effects on cells and tissues
  - Photosensitizing agent
  - Light of specific wavelength

Photodynamic Therapy (PDT)
The photodynamic therapy (PDT)

Application in dentistry
Process of Photodynamic therapy (PDT)
Low-density lipoprotein receptors in the uptake of tumour photosensitizers by human and rat transformed fibroblasts.

Polo L, Valduga G, Jori G, Reddi E.

Department of Biology, University of Padova, via U. Bassi 58/B, 35131 Padova, Italy.

Abstract

Low-density lipoproteins (LDL) increase the selectivity of tumour targeting by drugs, including sensitisers for photodynamic therapy, because of the enhanced expression of specific LDL receptors in many types of transformed as compared with non-transformed cells.
Photosesitizers

**Table 1** Currently available photosensitizers.

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<td>HpD</td>
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<td><a href="http://www.axcan.com">www.axcan.com</a></td>
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Photosensitizers

- Haematoporphyrins, HpD (Photofrine and others)
- Chlorines
  - Derivatives of Chlorophyll
- Porphycenes
  - Synthetic Porphyrines
Photofrin (Hematoporphyrinderivative, Hpd)

Photofrin is an approved clinical photosensitizer for photodynamic cancer therapy in Germany. It is mixture of oligomers of esterified and etherified hematoporphyrin. The figure below shows the chemical structure of Photofrin:
5-Aminolevulinic acid (Hematoporphyrin derivative)

5-ALA

Topical photodynamic therapy

Figure 2 Molecular structure for ALA.
Photodynamic Therapy with 5-ALA

• Most important Sensitizer in Dermatology is 5-ALA (5-Aminolaevulinic Acid)

• Is accumulated specifically in tumor cells

• Penetration depth only 2 mm

• Is used in treatment of actinic Keratosis, Basalioma, severe Akne, newly also in Cosmetics (USA)
5-ALA Absorption spectrum
Photodynamic diagnostic with blue-violet light (PDD)

Fuselage skin basal cell carcinoma in daylight

Fuselage skin basal cell carcinoma under wood light
The laser mouth shower

Indications:

- Pyorrhea
- Tooth and gums diseases
- Intraoral mucous membrane diseases
Photodynamic therapy of acne
Photodynamic therapy of acne
Photodynamic therapy for warts
Photodynamic skin rejuvenation
Photodynamic therapy of actinic keratosis
Photodynamic therapy of basal cell carcinoma
Photodynamic therapy of basal cell carcinoma
Photodynamic therapy of actinic keratosis
Photodynamic Therapy of actinic keratosis
Photodynamic therapy of actinic keratosis
Photodynamic therapy of ctinic keratosis
Photodynamic therapy of basal cell carcinoma

Basal cell carcinoma recurrence in a surgical scar
Findings after 2 treatments PDT
Photodynamic therapy of basal cell carcinoma

Ulcerated basal cell carcinoma before treatment

Findings after 1 treatment PDT
Systemic photodynamic therapy

Fotolone ( Chlorin E6 )

- Chlorin e6 as photosensitizer
- Indications
- current development status
Chlorin e6 Trisodium Salt

- a second generation photosensitizer for
  - systemic administration in oncologic indications
  - topical or systemic administration for the inactivation of bacteria/fungi
Chemical Properties

- trisodium salt of the „green“ porphyrin
- high solubility in water
- Molecular formula: $C_{34}H_{33}N_4Na_3O$
- High stability of the lyophilized API
Absorption spectrum of Chlorin E6
Properties of Chlorin e6 (Fotolon®)

- trisodium salt of the "green" porphyrin high solubility in water

- Molecular formula: $C_{34}H_{33}N_4Na_3O_6$
  Molecular weight: $596 + 3\times23$ g/mol

- 80% quantum yield

- Excitation wavelength $\sim 670$ nm

- High and selective accumulation in tumor cells (10:1) (plasma membrane, liposomes, intracellular vesicle)

- Drug light interval 3-4 h (for tumor) 5 min for vascular shut down

- After 48 h no drug left in normal tissue
Production

Natural sources (algae, grass, lucerne etc.)

FDA approved, GAP

inexhaustible availability (different sources/world-market)
GAP In accordance to GMP

GMP process:
- unique
- efficient
- highest purity
99% HPLC purity
PDD with Chlorin E6
Mode of action

3 – 4 h
Mode of action

1 – 15 min

PDT

Generation of singlet oxygen
Mode of action

24 – 48 h
- Apoptosis/
  Necrosis

PDT
Physical Properties

- 80% quantum yield
- Excitation wavelength ~ 670 nm

![Graph showing absorption and emission spectra with peaks at 405, 503, 533, 608.5, and 664 nm for PDD and 657 nm for PDT. The graph also shows emission peaks at 720 nm.]
Single Case studies: Dermatology

Actinic Keratosis:

PDD: 410 nm

PDT: 670 nm
# BCC, Fotolon® syst.

**EKL**
asermedicine, Elisabeth Deaconess Hospital  
laserm@elisabeth-klinik-berlin.de

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72h

10.2005 04.2006
Patient Ch.
Diagnosis: Lip carcinoma

Fotolon 2.5 mg/kg
Laser:
Wave length 666 nm,
E = 300 J/cm²

Prior to therapy

1 month after PDT

6 months after PDT
Patient Ch.
Diagnosis: Kaposi-Sarcoma

Prior to therapy
2 weeks after PDT
1 year after PDT

Fotolon 2.5 mg/kg
Laser:
Wave length 666 nm,
E = 300 J/cm²
Patient S.
Diagnosis: Vulvar carcinoma

Fotolon 2.5 mg/kg
Laser: Wavelength 666 nm, $E = 300$ J/cm$^2$

Prior to therapy

3 months after PDT
M. Bowen-PDT with Fotolon® syst.

Surrounding healthy tissue recovered within a week, the tumors developed into dry plaques on the forearms and head or exfoliative wounds in the anogenital regions.

Healing usually was completed usually one month after PDT.
Single Case studies (human): Urology
Single Case studies (human): Pulmology

Prior to PDT

48 h after PDT
The laser-needle body shower for PDT
External PDT of lymph metastases
Interstitial photodynamic therapy of liver metastases

T. J. Vogl (✉) · K. Eichler · M. G. Mack
S. Zangos · C. Herzog · A. Thalhammer
K. Engelmann
Department of Diagnostic and Interventional Radiology,
University of Frankfurt,
Interstitial photodynamic therapy of liver metastases
Interstitial photodynamic therapy of liver metastases
Interstitial PDT of lymph metastases
Interstitial PDT of lymph metastases
Interstitial PDT of squamous cell carcinoma
Interstitial treatment of tonsille cancer with metastases
Interstitial PDT of breast cancer with mediastinal metastases
Interstitial PDT of breast cancer with mediastinal metastases
Interstitial PDT of breast cancer with spinal metastases
Interstitial PDT with Chlorin E6 in liver cancer
Interstitial PDT with Chlorin E6 in liver cancer
Interstitial PDT of breast cancer
Interstitial PDT breast cancer
Brest cancer, PDD with blue light
Breast cancer PDD skin metastases
Interstitial PDT breast cancer
Bile duct cancer
Bile duct cancer
Kidney cancer
Pancreatic cancer
Pancreatic cancer
Pancreatic cancer
Pancreatic cancer
Case report pancreatic cancer

Diagnose:
Pankreaskopfkarzinom, ED 11/2011 mit
Z.n. pyloruserhaltender Pankreaskopfresektion
Port-Implantation am 23.8.2012
Adjuvante Chemotherapie mit Gemcitabin bis 08/12
Abgebrochene Chemotherapie wegen Unverträglichkeit
Einleitung einer Photosensitizerbehandlung 08/12
Rezidivierend transfusionspflichtige Tumoranämie
V.a. Peritonealkarzinose mit Ascitesbildung (CT 18.10.2012) sowie
Nachlaufendem Pleurerguss rechts mit wiederholter Entlastungspunktion
Anämie bei Neubildungen
Erneute kardiale Dekompensation mit Unterschenkelödemen und Lungenstauung,
NYHA III-IV
Art. Hypertonus
Rechtsschenkelblock
Hyperurikämie
Prostatahyperplasie
Case report pancreatic cancer
MRI 11/2011
Case report pancreatic cancer, MRI 11/11
Gemcitabin (Gemzar)
Sehr geehrter Herr Kollege,


**Diagnosen:**

Z. n. Pyloruserhaltender Pankreaskopresektion 11/2011 bei Pankreaskopfkarzinom pT1 pN1 pMx

Abbruch der postoperativen Chemotherapie mit Gemzar mono nach 20 Therapiezyklen (geplant waren 30)

**Interkurrente Eisenmangelanämie**

**Arterielle Hypertonie**


Besten Dank für die Zuweisung

Mit freundlichen Grüßen
Case report pancreatic cancer
MRI 8/12
Case report pancreatic cancer
MRI 8/12
External PDT of pancreatic cancer after Chlorin E6 application
Interstitial PDT of pancreatic cancer after Chlorin E6 application
Case report pancreatic cancer
MRI 12/12
Case report pancreatic cancer, MRI 12/12
Case report pancreatic cancer
tumor markers

Die Analysen Eisen (Photom.)/Ferritin (ECLI A) wurden am 21.02.13 per Schein nachgefordert.
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Perspectives on the Role of Photodynamic Therapy in the Treatment of Pancreatic Cancer

Wei Li et al., Xi‘an China
PDT in pancreatic cancer

Pancreatic cancer (PC) is one of the most lethal malignant diseases and has a dismal prognosis. It is estimated that over 37,000 patients were newly diagnosed with PC, and 34,000 patients died of this disease in the USA in 2010. PC has the lowest 5-year survival rate of any gastrointestinal tumor, and the median survival rate is no more than 6 months.
PDT in pancreatic cancer

PDT in combination with surgery, radiotherapy, chemotherapy, or antiangiogenic therapy has become a subject of research in recent years. This strategy still faces challenges, such as the reduction of side effects and the optimization of the method of treatment (i.e., multiple interstitial optical fibers to increase treated tumor volume), but it may become a superior method for treating PC. Another way to improve PDT is through the development of new photosensitizers.
PDT in pancreatic cancer

World Journal of Gastroenterology
Published online 2009 February 14.

Synergetic anticancer effect of combined gemcitabine and photodynamic therapy on pancreatic cancer in vivo

- Qi Xie, Cheng-Gang Wei, Department of Radiology, Nan Sha Center Hospital, Guangzhou, China
PDT in pancreatic cancer

- To investigate the anti-tumor effects of combined cytotoxic drug (gemcitabine) and photodynamic therapy (PDT) on human pancreatic cancer xenograft in nude mice.
- PDT has a significant anti-tumor effect, which is maintained for a short time and can be significantly enhanced by small doses of gemcitabine.
PDT in pancreatic cancer


Photodynamic therapy for cancer of the pancreas

Brown et al.
PDT in pancreatic cancer

Methods:
Patients were photosensitised with 0.15 mg/kg meso-tetrahydroxyphenyl chlorin intravenously. Three days later, light was delivered to the cancer percutaneously using fibres positioned under computerised tomographic guidance. Three had subsequent chemotherapy
PDT in pancreatic cancer

All patients had substantial tumour necrosis on scans after treatment. Fourteen of 16 left hospital within 10 days. The median survival time after photodynamic therapy was 9.5 months (range 4–30). Seven of 16 patients (44%) were alive one year after photodynamic therapy.
PDT in pancreatic cancer

This is the first report of the use of PDT to treat cancers of the pancreas. It has shown efficacy with a low morbidity and mortality. The technique may be of value for treating localised cancers in patients who are poor candidates for definitive surgery or in whom the location of the tumour makes pancreatic resection inappropriate. PDT can be used in conjunction with chemotherapy or radiotherapy.
Endoscopic PDT
Endoscopic PDT
Systemic PDT
new developments
5-Fluorouracil as a Phosensitiser

MIHAIL LUCIAN PASCU1, MIHAIL BREZEANU1, LETITIA VOICU1, ANGELA STAICU1, BENONE CARSTOCEA2 and RUXANDRA ANGELA PASCU2

1National Institute for Lasers, Plasma and Radiation Physics, Laser Department, P. O. Box MG-36, Bucharest – Magurele;
2Central Military Hospital, Ophthalmology Clinic, Bucharest, Romania

Abstract

5-FU exhibits a high fluorescence after irradiation with UV-vis light. An enhancement of the cytostatic activity of 5-FU under UV-vis irradiation was observed on an in vivo experimental model.
The tautomeric forms of 5-FU

Figure 1. *The pyrimidine ring and the two 5-FU tautomers: lactam and lactim forms.*
Capezitabine (Xeloda) low dose for oral PDT
Cis-Platin as photosensitizer

*Romanian Reports in Physics, Vol. 60, No. 3, P. 877–884, 2008*
*Dedicated to Prof. Ioan-Iovitz Popescu’s 75th Anniversary*

**INCREASE OF CISPLATIN THERAPEUTICAL INDEX THROUGH OPTICAL IRRADIATION: A CASE STUDY OF CHOROIDAL METASTASIS**

R. FUMAREL1, GABRIELA MURGOI1, P. ALBERT1, ANCA HURDUC1, M. L. PASCU2
Cis-Platin as photosensitizer

The reported study has pursued the increase of the therapeutical index of Cisplatin (cytotoxic agent frequently used in the chemotherapy of choroidal metastases) by exposure of the neoplastic tissue to a radiation emitted by a halogen lamp in spectral range 400–2000 nm.
Cis-Platin as photosensitizer

The use of optical irradiation makes it possible to use Cisplatin doses 10 times lower than in the conventional chemotherapy. That, in turn, generates minimal secondary effects (kidney toxicity) while increasing the antineoplastic effect of the drug.
Future therapy options

• Combination of

• PDT, systemic, local and interstitial
• Low dose Chemotherapy with photosensitive chemo drugs
• Immunotherapy (inravenous laser)
Hypericin as photosensitizer

St. John‘s wart plant
Hypericin as photosensitizer
Hypericin as photosensitizer
Hypericin as photosensitizer

• Hypericin can be regarded as the strongest natural photosensitizer

• Hypericin is only stimulated by yellow laser 589 nm

• Hypericin kills tumor cells, viruses and bacteria when irradiated by yellow laser light
A phase 1/2 study of orally administered synthetic hypericin for treatment of recurrent malignant gliomas.
Hypericin as photosensitizer

Figure 4. Mechanism of photoactivation of hypericin and induced damages.
Hypericin and photodynamic therapy decreases human pancreatic cancer in vitro and in vivo.

Liu CD, Kwan D, Saxton RE, McFadden DW.
Department of Surgery, UCLA Medical Center, Los Angeles, California 90095-6904, USA.

cdliu@mednet.ucla.edu
Hypericin PDT, effects of different wavelengths

![Graph showing tumor cell viability over exposure time for different wavelengths.](image)
Hypericin PDT, effects of different laser power
Inactivation of the Human Immunodeficiency Virus by Hypericin: Evidence for Photochemical Alterations of p24 and a Block in Uncoating
Hypericin for injection
Hypericin as photosensitizer in combination with yellow laser therapy
Hypericin as photosensitizer in combination with yellow laser therapy
Thank you !!!!