Photodynamic Therapy for Cancer

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ABSTRACT

Photodynamic therapy (PDT) is a promising local treatment modality based on the selective accumulation of a photosensitizer in malignant tissues and the subsequent irradiation with laser light. Photosensitizer is a substance that sensitizes an organism, cell, or tissue to light. It is an inherent part of PDT which, when absorbed by cancerous cells and exposed to light gets activated, killing cancer cells. Direct targeting of light source on hyperproliferative tissue and its preferential absorption at the targeted site gives PDT dual selectivity with minimal damage to adjacent normal tissues. The few PDT photosensitizers that have received official approval around the world are Photofrin®, Foscan®, Visudyne®, Levulan®, and most recently Metvix®. This review focuses on various aspects of PDT as an innovative site-directed therapy for cancer and other non-oncogenic diseases.

Keywords: Cancer, Photo-activation, Photodiagnostics, Photodynamic therapy, Photosensitizer, Targeted delivery, Tumor.

INTRODUCTION

The foundation of principle of the photodynamic effect was discovered in 3000 BC in India, Greece and Egypt however it was much later in 1980 that photoradiation therapy was investigated as a potential treatment modality for cancer. Photodynamic therapy (PDT) is basically a chemotherapeutic process using light-sensitive dye called photosensitizer (PS) that, after selective uptake and penetration of a neoplastic cell, is activated by a light source of specific wavelength (laser irradiation or light emitting diodes) inducing cell death. The cell destruction is the result of a photochemical excitation of PS that generates reactive oxygen species (singlet oxygen) that has a damaging effect on important cell organelles and biomolecules required for normal cell functioning. The normal cells remain unaffected due to sub-cellular localization of PS selectively in tumor cells.[1, 2] Apoptosis, necrosis and autophagy have all been identified as programmed cell death (PCD) mechanisms during PDT; apoptosis being the most preferred and common mechanism. So the most important components of a PDT are PSs, photo-activation and PCD.[3]

PDT is a two step procedure that uses photochemical reactions involving interaction of photosensitizing agents, light, and oxygen for the treatment of malignant or benign diseases. In step one; the photosensitizer is administered to the patient by topical, oral or intravenous route. It is then allowed to be taken up by the target cells. In the next step, activation of the photosensitizer occurs in presence of oxygen and a light of specific wavelength directed towards the target tissue. Direct targeting of light source on hyperproliferative tissue and its preferential absorption at the targeted site gives PDT its dual selectivity with minimal damage to adjacent normal tissues.[4] PDT can be used to treat some cancers or in pre-cancerous conditions when the affected area, or the tumor, is on or near the lining of internal organs like cancers or conditions that affect the oesophagus, head and neck, lung, mouth and skin (but not melanoma).[5]

History of photosensitizers and photodynamic therapy

The history of modern PDT goes back to the attempts of ancient Egyptians to treat skin diseases such as de-pigmented skin lesions (vitiligo) with light-absorbing compounds (herbal photosensitizers) applied through vegetable substances to produce photoreactions in tissues. Egyptians utilized natural photosensitizers such as psoralens from plants like parsnip, parsley, and Saint John's wort. After application of the powder to de-pigmented skin lesions, the person was exposed to bright sunlight. The sunrays activated the applied photosensitizers. As a result, the lesions became pigmented, an effect similar to a sunburn.

Photomedical procedures were also described as far back as 1550 BC in Ebers papyrus and the holy Indian Book Atharva Veda. At that time, black seeds of Beivechi (Veisuchaika) were applied for phototreatment of de-pigmented skin lesions followed by their exposure to direct sunlight. Later, Beivechi was identified as *Psoralena corylifolia* (Rapinat Herbarium, India, 1982). This plant contains psoralens (furocumarins), which are anaerobic photosensitizers. They also stimulate the production of pigment melanin in the skin. This favors the recovery of skin pigmentation. Psoralens can bring about photosensitization and photochemical reactions in the absence of oxygen. 8-Methoxypsoralen was the important active ingredient of psoralens.[6-8] Table 1 gives a detailed account of historical perspective of PDT and PS.

Principle of PDT

The mechanism by which the photosensitizers produce their killing effect on the host cells upon illumination by an appropriate light source is not precisely defined and is

the subject of continuing research. However, it is thought that there are at least two general mechanisms by which the photosensitizers are chemically altered upon illumination.

In the first general reaction mechanism, when PS is irradiated with a light of specific wavelength, it absorbs the visual light (700 and 850 nm) resulting in excitation of electron to the first short-lived excited singlet state followed by intersystem crossing during which changing of spin of excited electron occurs producing a longer-lived triplet state. Generation of reactive singlet oxygen $^1O_2$ then occurs as energy is transferred from PS triplet to the ground state triplet oxygen. The reactive oxygen ultimately induces necrosis and then directly destroys tumor cells (Figure 1).[18] The process by which biological damage occurs as a result of the optical excitation of a photosensitizer in the presence of oxygen is generally referred to as "photodynamic action". The short half-life of such reactive oxygen species (< 1 ps) is responsible for localized nature of the effect; and the modest energy

requirement. For photoactivation, the wavelength of light is matched to the electronic absorption spectrum of the PS so that it absorbs photons leading to a desired photochemical reaction. The range of activating light is typically between 600 and 900 nm.

The second general mechanism thought to be involved in the killing effect produced by certain photosensitizers involves the production of free radicals. Subsequent reactions of the radicals with organic molecules and/or with oxygen results in the biochemical destruction of the diseased tissue.

PDT offers inherent dual selectivity through selective uptake of PS in the neoplastic tissue and selective irradiation limited to a specified volume. Selectivity of PS has been further enhanced by binding them to molecular delivery systems that have high affinity for target tissue. The nature, location and quantity of PDT-induced reactions and the sensitivity of the target cells determine the outcome of the treatment.[19, 20]

Table 1: Historical perspective of PDT and PS

Principle	Reference	Year
Phototherapy was originated in India, Greece and Egypt.[9]	-	3000 BC
Discovery of oxygen dependent photodynamic reactions and further introduction of photodynamic reaction which is induced by excitation of photosensitizer when exposed to light.[9]	Raab *et al.*	1897-1898
Topical eosin used as a photosensitizer.[9]	Von tappeir	1903
Photodynamic term was introduced.[9]	Von tappeir	1907
Preparation of porphyrin mixture now known as hematoporphyrin derivative (HpD).[10]	Shwartz	1970
First photosensitizer photophrin was approved for clinical use.[11]	Dougherty *et al.*	1978
Treatment of skin tumors was first started by HpD and red light from a xenon arc lamp.[11]	Dougherty	1979
Broncho fiber scopic PDT was used for early stage central type squamous cell carcinoma.[12]	Keto *et al.*	1980
Second generation photosensitizers such as ALA known as porphyrin derivatives or synthetics were developed.[13]	-	1980
Photoimmunotherapy (PIT) was first introduced.[14]	Levy *et al.*	1983
ALA-induced porphyrin fluorescence labeled malignant glioma tissue was used for better visualization and to completely irradiate the tumor.[15]	Stummer *et al.*	1990
Water soluble chlorophyll such as chlorin p6 was first used for medical purposes.[16]	Snyder	1942
Tetrapyrrol chlorin-type macrocycles (chlorophyll A derivatives) were investigated in Russia to increase PDT efficiency. As a result, photosensitizers of the second generation were created. They were named Photochlorin and Photodithazine.[17]	-	1994-2004
Largest series of Photofrin-PDT for head and neck cancers of 107 patients was reported.[17]	Biel	1998
Actinic keratosis, a premalignant lesion became the first approved dermatologic indication of PDT where as ALA-PDT was also approved for moderate inflammatory acne vulgaris in US.[17]	-	2003

The fluorescence of photosensitizers

Photodynamic diagnosis (PDD) is based on the fluorescence effect exhibited by PSs upon irradiation and is often used concurrently with PDT to detect and locate tumors. Most photosensitizers emit some of the energy from the first excited singlet state as fluorescence. Since the emitted light is usually less energetic than the absorbed light, the emitted light is usually of higher

wavelength. Two different spectra are usually measured when the fluorescence properties of photosensitizers are evaluated, the fluorescence excitation and emission spectra. The fluorescence excitation spectra are obtained when the emission is detected at one wavelength, and the excitation wavelength is varied. For photosensitizers that are in their monomeric form (not aggregated), the fluorescence excitation spectra and absorption spectra are identical in shape. Aggregated photosensitizers

usually show low or no fluorescence. A fluorescence emission spectrum is obtained when the excitation wavelength is kept constant, and the wavelength for the detection of fluorescence is varied. The difference between the excitation and emission peak is called the Stoke's shift.[21]

Many photosensitizers preferentially accumulate in neoplastic tissues, and their fluorescence properties may be beneficial in the detection and diagnosis of such lesions. Each photosensitizer has its action spectrum and light should be applied at the wavelength of maximum absorption. For clinically used sensitizers this wavelength varies from 420 nm (blue) to 780 nm (deep red). Light waves of greater length penetrate tissue further: blue light attenuates greatly within 1-2 mm whereas red light can penetrate more than 5 mm. The treatment of deeper lesions therefore requires a photosensitizer that is activated at long wavelength. In addition, light of shorter wavelength is more likely to be absorbed by melanin and hemoglobin. Thus, most of the newer photosensitizers are excited by long wavelengths.

For detection of disease, the use of short wavelength light (i.e. blue or ultraviolet) allows the identification of abnormal areas by fluorescence. 5-aminolaevulinic acid (ALA), a precursor of the heme biosynthetic pathway, is increasingly being used for photodynamic detection because of its local conversion into natural photosensitizers. ALA is selectively taken up by dysplastic and malignant mucosa and this property has been exploited in the diagnosis of non-visible carcinoma-in-situ of the bladder, the detection of early stage lung cancer, the intra-operative assessment of resection margins in glioma surgery and nephron-sparing surgery for renal cell carcinoma.[22]

Photosensitizers

PS is a light-sensitive dye that upon uptake sensitizes an organism, cell, or tissue to light. It is an inherent part of PDT which, when absorbed by cancerous cells and exposed to light gets activated, killing cancer cells. All PSs require selective uptake and retention by cancer cells prior to activation by a light source and subsequent cell death induction.[23,24] The majority of PDT photosensitizers possess a heterocyclic ring structure similar to that of chlorophyll or heme in hemoglobin. Upon capturing light energy by the PS, a transfer and translation of light energy into chemical reaction in the presence of molecular oxygen produces singlet oxygen ($^1O_2$) or superoxide (O_2^-), and induces cell damage through direct and indirect cytotoxicity. Therefore, the PS is considered

to be a critical element in PDT procedures. Many PSs were introduced in the 1980s and 1990s. New ones are discovered and reported regularly.[24]

Classification of photosensitizers

PSs can be categorized by their chemical structures and origins (Table 2).[24,25]

In general, they can be divided into three broad families based on their chemical structure:

Porphyrin-based photosensitizers

Photofrin® (HpD), Levulan® (ALA), Metvix® (M-ALA), Visudyne® (Vertiporfin), Antrin® (Lutexaphyrin). Most of the currently approved clinical photosensitizers belong to this class.

Chlorophyll-based photosensitizers

a. Chlorins: Foscan® (Temoporfin), LS11® (Talaporfin), Photochlor® (HPPH)

b. Purpurins: Purlytin (tin-ethyl-etiopurpurin)

c. Bacteriochlorins

Dyes

a. Photosens® (Phtalocyanine)

PSs can also be classified on the basis of the year of their origin.[26]

1. First generation photosensitizers: porphyrins and those photosensitizers developed in the 1970s and early 1980s (*e.g.,* photofrin).

2. Second generation photosensitizers: porphyrin derivatives or synthetics made since the late 1980 (*e.g.,* ALA).

3. Third generation photosensitizers: generally refer to the modifications such as biologic conjugates (*e.g.,* antibody conjugate, liposome conjugate) with a built-in photo quenching or bleaching capability.

Ideal characteristics of photosensitizers[3]

Though it is difficult to get an ideal PS that satisfies all the criteria, there are some that either fulfills all or some criteria. These characteristics are laid out to make the comparison between them easier.

1. A high extinction coefficient

2. A high quantum yield of singlet oxygen

3. Commercially available in highest purity

4. Low dark toxicity but strong photocytotoxicity

5. Good selectivity towards target cells

6. Long-wavelength absorbing

7. Rapid removal from the body

8. Ease of administration though various routes

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Table 2: Important photosensitizers and their molecular targets[3, 26-31]

Category	Example	Area of localization	Molecular target	Application
Porphyrins (First generation photosensitizers) (1970)	Photofrin®	Golgi, plasma membrane	Vascular damage and ischemic tumor cell necrosis	Esophageal (including Barrett's) and bronchial cancer.
	Hemoporfin® (hematoporphyrin monomethyl ether, HMME)	---	Vascular damage and blood vessel occlusion	ocular as well as anti-tumor
Porphyrins (Second generation photosensitizers) (1980)	Tookad®	Vasculature	Vascular damage	In phase II/III clinical trials for prostate cancer.
	Foscan® (Mesotetra hydroxy phenyl chlorin)	Endoplasmic reticulum (ER), mitochondria	Vascular damage, tumor cytotoxicity	Head and neck cancer.
	Purlytin	Mitochondria, lysosomes	Tumor cytotoxicity	---
	Lutrin	Lysosome	Vascular damage, tumor cytotoxicity	---
	NPe6	Lysosome, endosome	Vascular stasis, tumor cytotoxicity	---
	Photosens®		Tissue penetration	Choroid and epibulbar melanoma
	Metvix® (Methyl ester of 5-ALA)	Mitochondria, cytosol, membranes	Tumor cytotoxicity	---
	Visudyne®	--		Age-related macular degeneration (AMD)
	Photoclor®	---	Poorer lymphatic drainage of the tumours, higher proliferation rates of tumour cells or leaky vasculature	In clinical trials for esophageal (including Barretts) and bronchial cancer
Chlorophyll-based photosensitizer	Chalcogenopyrylium dyes	Lysosome	Tumor cell cytotoxicity	---
Dyes	Phenothiazinium dye (Toluidine Blue)	ER, Golgi bodies	Tumor cell cytotoxicity	---
	Phenothiazinium dye (Nile blue and derivatives)	Lysosomes	Tumor cell cytotoxicity	---
	Cyanines	Mitochondria, plasma membrane	Tumor cell cytotoxicity	---
	ADPM06	ER, mitochondria	Vascular-targeted	---
Prodrugs	Levulan® (Aminolevulinic acid ; ALA)	Mitochondria, Cytosol, membranes	Tumor cytotoxicity	Skin cancers such as basal skin carcinoma and Bowen's disease
	Metvix® (Methyl ester of 5-ALA)	Mitochondria, cytosol, membranes	Tumor cytotoxicity	Actinic keratosis and basal cell carcinoma
Antibody conjugates (photoimmuno conjugates)(Third generation photosensitizers)	#Mylotarg® (drug-linked monoclonal antibody)	---	---	Cutaneous malignancies and AMD
LDL-complexed photosensitizers	Benzoporphyrin derivative monoacid A (BPD-MA) complexed with LDL	----	----	---

withdrawn from the market

A few PDT photosensitizers that have received official approval around the world[17] are Photofrin® (porfimer sodium; Axcan Pharma, Inc.), Foscan® (temoporfin, meta-tetrahydroxyphenylchlorin, mTHPC; Biolitec AG), Visudyne® (verteporfin, benzoporphyrin derivative monoacid ring A, BPD-MA; Novartis Pharmaceuticals), Levulan® (5-aminolevulinic acid, ALA; DUSA Pharmaceuticals, Inc.), and most recently Metvix® (methyl aminolevulinate, MLA or M-ALA; PhotoCure ASA.).

Several promising PSs currently under clinical trials [17] are HPPH (2-[1-hexyloxyethyl]-2-devinyl pyropheophorbide-a, Photochlor; Rosewell Park Cancer Institute), motexafin lutetium (MLu, lutetium(III) texaphyrin, Lu-Tex, Antrin; Pharmacyclics Inc.), NPe6 (mono-L-aspartyl chlorin e6, taporfin sodium, talaporfin, LS11; Light Science Corporation), SnET2 (tin ethyl etiopurpurin, Sn etiopurpurin, rostaporfin, Photrex; Miravant Medical Technologies).

The pharmacokinetics of any PS depends on a variety of factors.[32] These range from aggregation–deaggregation equilibria in the blood, binding to serum components, binding to and penetration through the blood vessel wall, diffusion through the organ/tumor parenchyma, potential metabolization and finally excretion. In principle the quantification of PS in tissue and blood is easy due to their fluorescence.

PDT *versus* conventional therapy

PDT has several attractive features over conventional methods for treating cancer such as chemotherapy, radiation and surgical procedures. In the conventional cancer chemotherapy along with the cancerous cells, normal healthy cells are also killed but the most attractive features of PDT are its selective uptake by specific tissue layers, localization of drug to hyper proliferating tissue along with localized cytotoxicity and the precision of the laser light directed *via* optical fibers. Also photosensitizers utilized are generally non-toxic, concentrate or remain preferentially in cancer cells and can be utilized with other modes of treatment since PDT does not interfere with other chemicals or processes.[33] Most importantly, repeated use of PDT does not lead to resistance. The mechanical and functional integrity of the organ remains unaffected as scarring of connective tissues, including collagen and elastin does not occur. PDT is said to be more selective than hyperthermic ablation in causing tissue necrosis. The cost of PDT was estimated to be at least 30 percent less than the cost of surgery so it is cost effective also.[34] The search for new photosensitizers, new laser and non-laser light treatments, and ways of reducing the side effects is a continuous process and many are under clinical trials.[35]

Irrespective of many advantages offered by PDT, many of the PSs produce various side effects which limit their use. The most predominant side effect is the development of uncontrolled photosensitivity reactions in patients after the systemic administration of the PS and the exposure of

the patient to normal sunlight. So on exposure to the sun, the patients undergoing PDT can develop generalized skin photosensitization. As a result, the patient after receiving systemic injections of a PS is required to avoid bright light, especially sunlight for periods of about four to eight weeks. Furthermore, since many of the PSs bind to other non-cancerous cells, some healthy cell destruction can also occur.

Profiles of important photosensitizers

Porfimer sodium (Photofrin®)

It is a first generation, porphyrin-based photosensitizer chemically known as 2-[1-hexyloxyethyl]-2-devinyl pyropheophorbide-a. It is a hematoporphyrin derivative (HpD). It is the only FDA-approved drug for the curative therapy of solid tumors. It suffers from certain disadvantages: its complex chemical nature; retention by skin and less than optimal photo-physical properties. It is a highly lipophilic agent that is concentrated in plasma and is nearly 100% bound to plasma proteins. No instances of cutaneous photosensitivity have been noted for this clinical anticancer PDT agent.[36]

Advantages of Photofrin® are that it is a reliable, pain-free, relatively safe and non-toxic PS. But main drawback is that it is not highly selective at 2 mg/kg and has significantly prolonged photosensitivity. Without active intervention, patients need to stay out of sunlight for at least 4 weeks.

PHOTOFRIN® (Porfimer sodium)
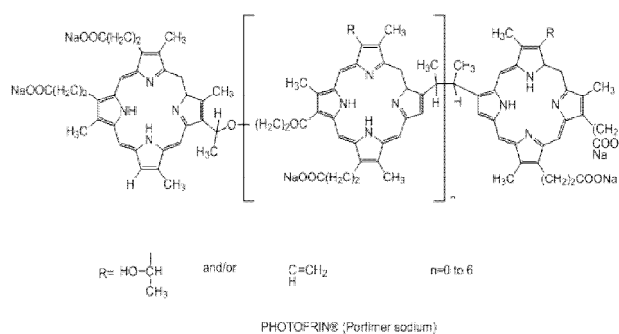
Porfimer sodium, sold as Photofrin®, is an injectable photosensitizer used in photodynamic therapy, radiation therapy and for palliative treatment of obstructing endobronchial non-small cell lung carcinoma and obstructing esophageal cancer and pre-malignant conditions (high-grade dysplasia in Barrett's esophagus). Porfimer is a mixture of monomers, dimers, and oligomers derived from chemical manipulation of hematoporphyrin formed by ether and ester linkages of up to eight porphyrin units.[37] In practice, a red light source emitting at 630 nm is used to excite the Porfimer oligomers.[38] Half-life of Photofrin® is 21.5 days (mean) and 90% of the drug is protein bound. Photofrin®clears from a variety of tissues within 40 to 72 h after administration. Photofrin® remains longer in tumor tissue. Skin and organs of the reticulo-endothelial system (including the liver and spleen) also retain Photofrin® for longer than 40 to 72 h after administration.[37-39]

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Mechanism of action

Photofrin®is intravenously administered and selectively accumulates in cancer cells and dysplastic tissue. The cytotoxic and antitumor actions of Photofrin® are light and oxygen dependent. It is a 2-stage process. Tumor, skin, and organs of the reticulo-endothelial system (including liver and spleen) retain Photofrin® for a longer period. Illumination with 630 nm wavelength laser light (red light) constitutes the second and final stage of therapy. Tumor selectivity in treatment occurs through a combination of selective retention of Photofrin® and selective delivery of light. The application of red light activates Photofrin® to an excited state. Energy is transformed from Photofrin® to generate singlet molecular oxygen. This results in the production of superoxide and hydroxyl radicals. Excited Photofrin®-mediated vasoconstriction, platelet aggregation and clotting lead to vascular occlusion. Ultimately, ischemic necrosis occurs secondary to vascular occlusion. This may be partially mediated by the local release of thromboxane A2. The necrotic activity and associated inflammatory processes may evolve over several days. The end result is cellular damage by lysis of cancer cells, ischemic necrosis of tumors, and dysplastic tissue. The laser treatment induces a photochemical, not a thermal effect. [39, 40]

Adverse reactions

Photofrin® is a relatively safe drug. Most common adverse reactions reported during clinical trials (>10% of patients) are:[39]

In patients with osophageal cancer: Anemia, pleural effusion, pyrexia, constipation, nausea, chest pain, pain, abdominal pain, dyspnoea, photosensitivity reaction, pneumonia, vomiting, insomnia, back pain, pharyngitis.

In patients of obstructing endobronchial cancer: Dyspnoea, photosensitivity reaction, hemoptysis, pyrexia, cough, pneumonia.

In patients treated for superficial endobronchial tumors: Exudate, photosensitivity reaction, bronchial obstruction, edema, bronchostenosis.

In patients of high-grade dysplasia in Barrett's esophagus: Photosensitivity reaction, esophageal stenosis, vomiting, chest pain, nausea, pyrexia, constipation, dysphagia, abdominal pain, pleural effusion, dehydration.

If PDT is to be used before or after radiotherapy, sufficient time should be allotted between the two therapies to ensure that the inflammatory response produced by the first treatment has subsided before commencing the second treatment. If PDT is to be given after radiotherapy, the acute inflammatory reaction from radiotherapy usually subsides within four weeks after completing radiotherapy, after which PDT may be given.

In the US, Photofrin® is FDA approved for early and late endobronchial lesions as well as high-grade dysplasia associated Barrett's esophagus and esophageal obstructing lesions. Other clinical applications of Photofrin® are mainly in papillary bladder cancer. [41]

Temoporfin (FOSCAN®)

5,10,15,20-Tetra (m-hydroxyphenyl)chlorin (mTHPC) with the generic name "temoporfin" and the proprietary name "Foscan®" is one of the promising reduced porphyrins which has been the subject of investigations by a number of research groups for almost two decades. It is a member of the chlorin family with a number of promising features due to which it has received lot of attention on the clinical front. Now, temoporfin has reached an exciting state of development as it has gone through the requisite clinical testing and is regarded as an established cancer drug on the market.[42-45] It is mainly used as PDT for the treatment of squamous cell carcinoma of the head and neck. It is photo activated at 652-660 nm giving it greater depth of penetration. The drug is dosed at 0.15 mg/kg intravenously and is associated with pain.[46, 47] It is a very efficient PS with short treatment time.

Initially, Scotia Pharmaceuticals Ltd. U. K., developed this drug, first in collaboration with Boehringer Ingelheim and in 1999 was granted orphan drug status by the U.S. F.D.A and was accepted for marketing review by the European Medicines Evaluation Agency (EMEA). In 2000, it was granted fast track review status by the F.D.A. Nevertheless, approval by the F.D.A. was declined in September 2000, and then in January 2001 by the EMEA. Later an appeal to the EMEA was successful in June 2001 and in 2001 marketing authorization was given as a local therapy for the palliative treatment of patients with advanced head and neck cancer who have failed prior therapies and are unsuitable for radiotherapy, surgery or systemic chemotherapy and further uses.[48]

FOSCAN® (Temoporfin)

The pharmacokinetics of mTHPC in humans was evaluated thoroughly in 1996 in a clinical study with concentration measurements of plasma, cancer and normal tissue biopsies. After drug delivery, blood was taken in periodic time intervals and biopsies were taken immediately prior to PDT from 25 patients who suffered from various cancers. The maximum concentration of mTHPC in blood was reached by 10–24 h which distinguishes Foscan® from other drugs when delivered directly into the blood cycle. Depending on the study a half-life of the drug of 30–45 h was established. Probably, it is initially accumulated in the liver followed by a slow release mechanism.[49, 50]

Mechanism of action

A study by Kessel in 1999 showed that illumination of murine leukemia cells treated with *m*THPC resulted in the release of cytochrome *c* and activation of caspase-3 resulting in an apoptotic response. Mitochondrial damage and cytochrome *c* release was also described for other myeloid leukemia cells, human colon adenocarcinoma cells and squamous cell carcinomas. Later Bezdetnaya and coworkers showed that the ER and Golgi are the sites of the primary effects. They clearly showed that enzymes in the Golgi, such as uridine 5'-diphosphate galactosyl transferase, or in the ER, such as NADH cytochrome *c* reductase, are inactivated through PDT treatment, while mitochondrial marker enzymes (cytochrome *c* oxidase and dehydrogenases) were unaffected.[51] Several studies have indicated that *m*THPC results in less photosensitivity than Photofrin®.[52]

Adverse reactions

As this drug is very active and is usually infused 4 days prior to therapy, patients can suffer from heightened photosensitivity even out of direct exposure to sunlight (room temperature) which can last at least 1 week post-treatment as well. This is the major clinical drawback of this drug though theoretically it appears to be efficient with high level of light penetration and fast metabolism. So patients need to be treated in a dark room; and high intensity O.R. lighting must be avoided. This light hypersensitivity is generally minimized by following medical advice.[53] To reduce the risk to patients several types of creams have been tested on patients and, for example, dark cover cream promises acceptable protection. Other side effects are mild to moderate pain in the treated area. [54]

*m*THPC finds wide application in gynaecological diseases [55], head and neck cancer[56], skin cancer[57], gastrointestinal and esophageal cancers[58-61], brain cancer[62], prostate cancer[63-66], pancreatic cancer[67], breast cancer[68], urological malignancies[69] and pulmonary tumors.[70-75]

Hypericin

Hypericin is a naphthodianthrone, a red-colored anthraquinone-derivative, and the natural photoactive pigment which, together with hyperforin, is one of the principal active constituents of *Hypericum perforatum* plants (Saint John's wort).[76-81] It can also be synthesized from the anthraquinone derivative emodin.[82]
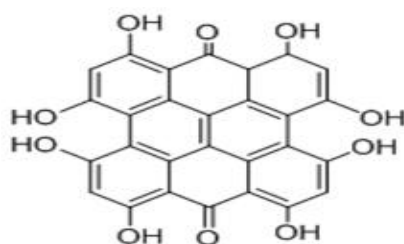

Hypericin

Mechanism of action

Hypericin (HY) is a highly lipophilic drug with binding affinity for phospholipids, plasma proteins and tumors therefore targets mainly the cell membranes. In number of studies using HY for the treatment of bladder cancer 82-94% sensitivity and 91-98.5% specificity has been observed. It is retained in the tumor for at least 1 h. Hypericin gives its action by photohemolysis of red blood cells. It induces apoptosis and necrosis in a concentration, oxygen and light-dose dependent manner.[77, 83] Its photodynamic potency is similar to other sensitizers such as hematoporphyrin, chlorophyll, rose Bengal and erythrosine B in visible light. The antibacterial and antiviral effects of hypericin are also believed to arise from its ability for photo-oxidation of cells and viral particles. [84]

Verteporfin (Visudyne®)

Verteporfin is a benzoporphyrin derivative of porphyrin which is clinically active when formulated with liposomes. [85, 86] It is available as Visudyne® by Novartis Pharmaceuticals. Its photo-activation occurs at 690 nm allowing for deeper penetration and activation with an onset of 15—30 min after injection. It has rapid accumulation and clearance so that skin photosensitization is minimal.[87]
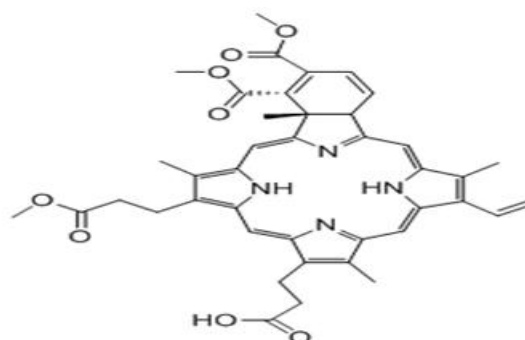
VISUDYNE® (Verteporfin)

Mechanism of action

Verteporfin sensitization is based on vascular disruption and shutdown. The drug therefore targets lesions (hemorrhaging neovascular vessels supplying to choroids of the eye) where neovasculature is involved in the pathophysiology. [88, 89] When verteporfin (6 mg/kg i.v. with 100 J/cm2 illumination) is applied to leaky vessels in the eye, within 30 min of infusion, neovascular occlusion generally occurs and visual loss is curtailed.

Verteporfin has been successful as treatment for age related blindness, choroidal neovascularization due to serous chorioretinopathy[90], neovascularization due to pathologic myopia[91], choroidal melanoma that failed prior treatment[92, 93] and Cutaneous lesions. [94]

Adverse effects

Pain on photosensitizer infusion is the main common side effect.

HPPH (Photochlor®)

HPPH (Photochlor®) manufactured by RPCI is a chlorin-based hydrophobic lipophilic photosensitizer[95] that undergoes photo-activation at 665nm. The dose is 0.15 mg/kg i.v. with a light dose at 48 h, of 150 J/cm. Excellent response was observed in a number of naturally occurring tumors in dogs and cats[96, 97] and in esophageal cancers. Basal cell lesions, Barrett's esophagus, endobronchial recurrence from lung cancer, may also be treated successfully. Main attractive features were minimal sunlight photosensitivity, excellent activity and relative safety, with which one may expect this to become a significant PS in the clinic.[98]

PHOTOCHLOR® (HPPH)
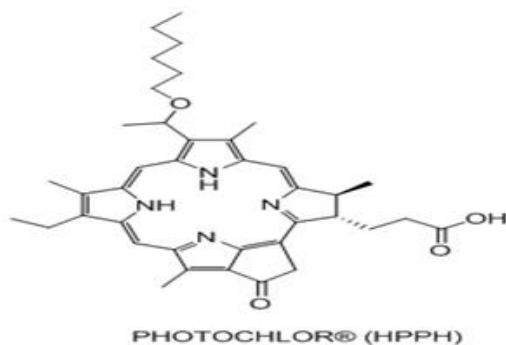
Lutexaphyrin (Antrin®)

Lutexaphyrin available as Antrin® by Pharmacylics belongs to the class texaphyrins. Lutetium texaphyrin is known by several names such as Lu-tex or OptrinTM for cutaneous formulations and Antrin® for vascular (cardiac, peripheral, ophthalmic) formulations. It is a water-soluble PS that photo activates at 730 nm resulting in deep light penetration. It accumulates in neoplastic tissues and neovasculature and has binding affinity for low-density lipoproteins, so it may be effective against artherosclerotic plaque. Its clearance is in hours, so extent of photosensitivity is reduced.

ANTRIN® (Lutexaphyrin)
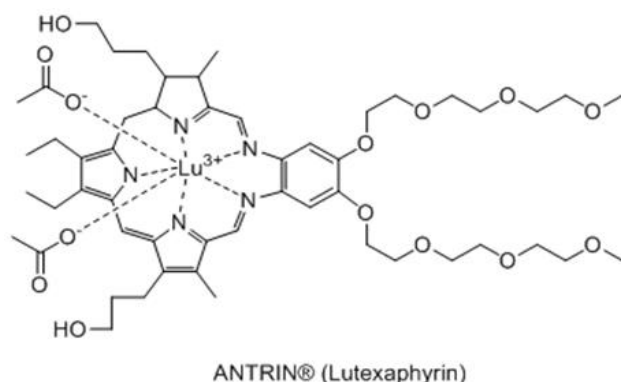
Texaphyrins are synthetic expanded porphyrins with unique properties. Most of them contain paramagnetic metal ion, gadolinium in their structures. For many years they were used as imaging aids in MRI[99] and can be used as radiation sensitizes also. They have been looked upon as the photosensitizers of the future.[99-101] Motexafin gadolinium is another PS belonging to the class of texaphyrins. Motexafin lutetium was employed

successfully for Cutaneous metastasis from breast cancer.[102, 103]

Photoactive dyes

Ben-Hur *et al.* were the first to report potential use of phthalocyanines as photosensitizers in 1985.[104] Since then dyes have been considered as a fertile ground to develop successful photosensitizers. Phtalocyanines and napthalcyanines are two such classes of photoactive dyes that have been explored for development of PSs.[105-107]

Their photo activation occurs between 650—850nm range at energies around 100 J/cm2. Hydrophobic nature of these dyes calls for use of delivery systems such as liposomes. They have been linked with a variety of metals like aluminum, zinc, and silicon to improve efficacy. Linkage with metals results in stable chelates with enhanced photosensitizing tumoricidal activity.[108]

Phthalocyanines are structurally similar to the porphyrin family. Chemically phthalocyanines are azaporphyrins consisting of four benzoindole nuclei connected by nitrogen bridges in a 16-membered ring of alternating carbon and nitrogen atoms around a central metal atom which form stable chelates with metal cations. In these compounds, the ring center is occupied by a metal ion (such as a diamagnetic or a paramagnetic ion) that may, depending on the ion, carry one or two simple ligands. In addition, the ring periphery may be either unsubstituted or substituted.
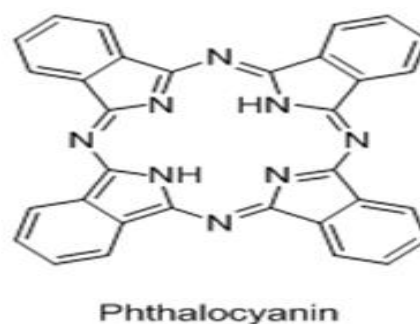
Phthalocyanin

Unlike some of the porphyrin compounds, phthalocyanines strongly absorb clinically useful red light.[109] The greater absorption of red light by the phthalocyanines over porphyrins indicates deeper potential penetration. Phthalocyanines are relatively easy to synthesize, purify, and characterize in contrast to the porphyrins, which are often difficult to prepare. Certain metallic phthalocyanines, such as aluminum phthalocyanine tetrasulfonate (AlPcS) and chloroaluminum phthalocyanine (AlPcCl), offer a number of advantages over porphyrins as therapeutic agents for PDT. Metal-free phthalocyanines show poor photodynamic activity[109-111] as do phthalocyanines containing paramagnetic metals. In contrast, those containing diamagnetic metals, such as Al, Sn, and Zn, are active as a result of the long half-life of the triplet state.[110, 111] While in general there appears to be an increase in photosensitizing ability with lipophilicity,[112]

some highly lipophilic derivatives, such as a tetraneopentoxy derivative, are poor photosensitizers.[113]

Photosens® (General Physics Institute), a sulfonated aluminum phthalocyanine, has been clinically successful in a wide variety of cutaneous and endobronchial lesions. It has been used to treat malignancy and infection[114] and also in head and neck tumors including the lip, pharynx, larynx, and tongue.[115, 116]

Photosensitizer Prodrugs

δ-Aminolevulinic acid

Aminolevulinic acid (5-amino-4-oxopentanoic acid or ALA) is an endogenous metabolite normally formed in the mitochondria and eight ALA molecules on conjugation form the natural photosensitizer protoporphyrin IX (PpIX). The latter is ultimately converted into heme. The rate-limiting enzyme ferrochelatase converts PpIX to its downstream substrates. Externally administered ALA is photo dynamically inactive, non-selective and non-toxic PS which then undergoes intracellular bioconversion, producing abundant PpIX which is not quickly converted to its final product - heme by ferrochelatase and therefore accumulates within cells. PpIX is a potent photosensitizer and hence ALA becomes one of the most successful bio precursor Prodrugs of PpIX used in cancer treatment. This is an already approved therapeutic strategy in PDT. Illumination of the tumor site with red light activates PpIX, triggers the oxidative damage and induces cytotoxicity.[117-121]

For therapeutic purposes ALA is administered topically or systemically and penetrates non-selectively into all cells, where it is bioactivated by the enzymes of the heme biosynthesis pathway to an active sensitizer PpIX. These enzymes are expressed by nearly all human cells but more so in tumors as compared to normal healthy cells which actually is responsible for higher accumulation and selectivity of PpIX in the abnormal cells.[122]

Rapid metabolism, fast systemic clearance of ALA-induced PpIX within 24 h without the risk of overexposure to prolonged photosensitivity, high selectivity for malignant lesions without damaging normal cells and possibility of frequent dosing (every 48h) without cumulative effects are the most significant advantages of ALA. Moreover ALA-PDT has demonstrated high efficacy, minimal side effects and excellent cosmetic effects in a wide range of benign and malignant conditions.[47, 123]

ALA-PDT also offers many advantages over traditional antitumor treatments, the most important being absence of immunosuppressant side effect, lack of intrinsic resistance mechanisms to $^1O_2$- induced cytotoxicity, reduced long-term morbidity and the possibility of repeated treatment. ALA-PDT seems to be the most successful prodrug treatment in clinical oncology.

Bioavailability of oral ALA is generally lower (60%) than after intravenous administration owing to presystemic drug elimination. Large capacity of gastrointestinal

mucosal cells to biosynthesize PpIX and hepatic first pass metabolism are two major factors responsible for the reduction of ALA bioavailability.[124] For the treatment of bladder cancer ALA is administered intravesically as it results in improved bioavailability. The bladder concentration of ALA is approximately 20,000-fold higher in comparison to the systemic circulation. Moreover, only 1% of the intravesical dose is absorbed from the bladder by the systemic circulation. Therefore, after intravesical ALA administration, no systemic phototoxicity is observed.[124, 125] On the other hand, preferential mucosal accumulation of PpIX might be favorable in the treatment of tumors of the gastrointestinal tract. Also, limited PpIX accumulation in the underlying stroma may reduce damage of deeper layers and risk of perforation or stenosis.[125]
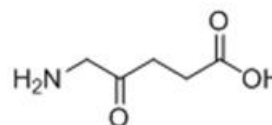

LEVULAN® (Aminolevulinic acid)

Adverse effects

Although ALA-PDT is generally well tolerated, some patients complain of stinging, burning, pricking, smarting and itching pain during PDT and several hours after irradiation.[126] A disagreeable pain or a history of previous experience of long-lasting pain may be managed with cyclooxygenase (COX) antagonists, especially COX-2 inhibitors that seem to potentiate antitumor effects of PDT. Other rare adverse effects associated with ALA administration include nausea, fatigue, paraesthesia and headache.[127, 128]

Methyl aminolevulinate (Metvix®)

Methyl aminolevulinate (MAL), a methyl ester of aminolevulinic acid, has been used effectively as a topical photosensitizing agent in PDT of epidermal lesions such as AK and basal cell carcinoma (BCC). The optimal regimen for MAL-PDT (as used in all clinical trials) is MAL 160 mg/g applied for 3 h before illumination with red light (570-670 nm) at a total light dose of 75 J/cm^2, as determined in dose-finding trials. In randomized, multicenter, phase III clinical trials, treatment with MAL-PDT resulted in a complete response (i.e. complete disappearance) in up to 91% of AK lesions and up to 97% of BCC lesions.[129] Methyl aminolevulinate is a prodrug that is metabolized to protoporphyrin IX (a PS) used in PDT.[130, 131]
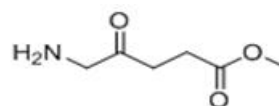

METVIX® (Methyl aminolevulinate)

After topical application of methyl aminolevulinate, porphyrins will accumulate intracellularly in the treated skin lesions. The intracellular porphyrins (including PpIX)

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upon light activation in the presence of oxygen, form singlet oxygen which causes damage to cellular compartments, in particular the mitochondria.[130]

Hexaminolevulinate hydrochloride (Cysview®)

The generic name of Cysview® is hexaminolevulinate hydrochloride. Hexaaminolevulinate is an ester prodrug of PpIX.[131] It is marketed in the dosage form of intravesical solution. Cysview® is a trademark of Photocure ASA. Cysview® is an optical imaging agent indicated for use in the cystoscopic detection of non-muscle invasive papillary cancer of the bladder among patients suspected or known to have lesion(s) on the basis of a prior cystoscopy. Cysview® is used with the Karl Storz D-Light C Photodynamic Diagnostic (PDD) system to perform cystoscopy with the blue light setting (Mode 2) as an adjunct to the white light setting (Mode 1). So basically Cysview® is used as photodynamic diagnostic rather than PDT for cancer.[132, 133]
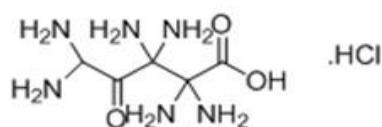
CYSVIEW ® (hexaminolevulinate hydrochloride)

On 28 May 2010 the U.S.-F.D.A. approved Cysview® for the detection of non-muscle-invasive papillary cancer of the bladder in patients with known or suspected bladder cancer.[134] *In vitro* studies have shown increased porphyrin fluorescence in normal urothelium after exposure to Cysview®. In the human bladder, a greater accumulation of porphyrins is proposed in neoplastic or inflamed cells, compared to normal urothelium. After bladder instillation of Cysview® for approximately 1 h and subsequent illumination with blue light at wavelengths 360 – 450 nm, the porphyrins fluoresce red. After bladder instillation of [^{14}C]-labeled Cysview® (100 mg) for approximately 1 h in healthy volunteers, absolute bioavailability of Cysview® was 7%. It shows biphasic elimination, with an initial elimination half-life of 39 min, followed by a terminal half-life of approximately 76 h. Whole blood analysis has shown no evidence of significant binding of Cysview® to erythrocytes. An *in vitro* study showed that Cysview® underwent rapid metabolism in human blood.[132, 133]

Mechanism of action

Hexaminolevulinate is an ester of aminolevulinic acid, a heme precursor; used as photoactive intermediate protoporphyrin IX (PpIX) and other photoactive porphyrins (PAPs); PpIX and PAPs preferentially accumulate in neoplastic cells and are detected at light wavelengths of 360-450 nm to distinguish between cancerous and normal tissue. PpIX and PAPs are reported to accumulate preferentially in neoplastic cells as compared to normal urothelium, partly due to altered enzymatic activity in the neoplastic cells. After excitation with light at wavelengths between 360 and 450 nm, PpIX and other PAPs return to a lower energy level by

fluorescing, which can be detected and used for cystoscopic detection of lesions. The fluorescence from tumor tissue appears bright red and demarcated, whereas the background normal tissue appears dark blue. Similar processes may occur in inflamed cells.[132, 133, 135]

Adverse effects

Dysuria, hematuria, headache, pain, urinary retention and spasm are the adverse effects of Cysview®.[135]

Applications of photodynamic therapy

PDT has many applications in a wide range of fields from preclinical to clinical medical science. PDT is mainly used in oncologic diseases and has been used successfully for the treatment of a broad range of cancers including metastatic breast tumors, endometrial carcinomas, bladder tumors, malignant melanoma, Kaposi's sarcoma, basal cell carcinoma, chondrosarcoma, squamous cell carcinoma, prostate carcinoma, laryngeal papillomas, mycosis fungoides, superficial cancer of the tracheobronchial tree, cutaneous/mucosal papilloma, gastric cancer and enteric cancer. PDT also finds applications in nononcologic diseases such as psoriasis, macular degeneration of the retina, atherosclerotic plaque and restenosis, bone marrow purging for treatment of leukemias with autologous bone marrow transplantation, inactivation of viruses in blood or blood products and several autoimmune conditions, including rheumatoid arthritis.[136,137] Compared to normal tissues, most types of cancers are especially active in both the uptake and accumulation of photosensitizer agents, which makes cancer especially vulnerable to PDT.[138-140] Since photosensitizers can also have a high affinity for vascular endothelial cells, PDT can be targeted to the blood carrying vasculature that supplies nutrients to tumors, increasing further the destruction of tumors.[141,142]

Dermatology

Preliminary trials on Porfimer sodium suggest a role for PDT in the treatment of primary, recurrent, and metastatic nonmelanoma skin cancers. Both HPD and porfimer sodium appear to be limited by generalized Cutaneous photosensitivity, which lasts up to 6 to 8 weeks after administration. Verteporfin (BPD) has shown promise in clinical studies as a safe and effective photosensitizer for PDT of non-melanoma cutaneous malignancies. The use of verteporfin for PDT of nononcologic conditions has also been studied. Recent trials have shown efficacy in the treatment of psoriasis by BPD-sensitized PDT using drug and light doses lower than those used for malignant tumors.[93]

Actinic keratoses (AK)

Both ALA and MAL are approved in several countries, including the U.S. by the F.D.A., for the treatment of AK. In the F.D.A.-approved protocol, ALA is to be applied on AKs only, followed 14-18 h later by 10 J/cm2 of blue light

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exposure. For the treatment of AK with MAL, the cream is applied on lesions following skin preparation. Skin preparation consists of removal of the crusts or hyperkeratotic portion of the AK with a curette, which probably enhances MAL penetration. MAL is then applied under occlusion for a period of 3 h, followed by exposure to 37 J/cm2 or 75 J/cm2 of red light. The European labeling suggests using a single MAL- PD session, although this can be repeated 3 months later for lesions that do not completely respond. The F.D.A.-approved protocol suggests using 2 MAL-PD sessions conducted 7 days apart.[143-149]

Basal cell carcinoma (BCC)

A number of small studies have been published using ALA-PDT for the treatment of BCC. However, these studies used varying ALA formulations, concentrations, penetration enhancers, light sources, and time between ALA application and light exposure. These studies have shown short-term complete response rates ranging from 59-92% and recurrence rates ranging from 5-44%, with a tendency towards lower clearance rates for nodular BCC. These variations in response are probably related to the different protocols and techniques used. Only MAL has been studied with standardized protocols in phase 3 multicenter trials for the treatment of BCC. In all these studies, a gentle curettage was performed to remove crusts before MAL application. Studies show histological cure rates at 3 months to be 85% for superficial BCC and 75% for nodular BCC. At 24 months after treatment, lesion recurrence rates (recurrence in lesions that initially showed a complete response) have been reported to be 18%. Five-year follow-up data recently presented at meetings show that most recurrences following MAL-PDT for superficial or nodular BCC occur during the first 2 years after PD. A consistent finding in MAL–PDT studies for BCC is that the cosmetic outcome has been shown to be superior to surgery or cryotherapy.[150] Metvix® is also used effectively for treatment of basal cell carcinoma.[151]

Acne

ALA-PDT is currently used off-label for the treatment of acne. Significant clinical improvement and a decrease in sebum production and sebaceous gland size have been shown post treatment. Histological analysis showed destruction of sebaceous glands, which suggests that this therapy has the potential for long term improvement of acne. Additional small studies using various light sources, including the Blu-U and intense pulse light, have also been published and suggest that ALA-PDT has efficacy for the treatment of acne. Physicians currently using ALA-PDT for the treatment of acne use a short incubation time of 30-60 minutes followed by light exposure, mostly from a Blu-U or an intense pulse light device. Pulse dye lasers can also be used, although the spectral output of the pulse dye laser is not ideal to match the excitation spectrum of protoporphyrin IX. Multiple sessions may provide a better improvement; however, the exact frequency and number of sessions required to optimize the treatment is

currently unknown. The importance of using red versus blue light has not been thoroughly studied, but given that sebaceous glands are often located in the mid dermis, red light might be a better choice to target these glands.[152-156] PDT is currently in clinical trials to be used as a treatment for severe acne.[157]

Bowen's disease (BD)

BD is considered as an early stage or intraepidermal form of squamous cell carcinoma. Both ALA and MAL have been shown to induce good clinical responses in persons with BD. MAL has been approved in Europe for the treatment of BD when surgical excision is considered less appropriate. BD might be one of the best clinical indications for PDT because the lesions often are large and the surgical approach may result in extensive scarring.[158-162]

Gastroenterology

Esophageal carcinoma usually is diagnosed at an advanced, incurable stage. PDT with porfimer sodium is thought to have a direct toxic effect on malignant cells *via* the production of singlet oxygen, which damages the microvasculature of the tumor and renders it ischemic. The 630 nm wavelength used for clinical PDT exhibits the greatest relative degree of light penetration into tissue, with corresponding activation of retained photosensitizer. The efficacy of PDT with porfimer sodium is closely related to the stage of disease. PDT has been shown to be potentially curative in patients with early, noninvasive tumors of both squamous and glandular (adenocarcinoma) histologies. PDT appears to have the added advantages of fewer treatments and less pain. The role of PDT in gastrointestinal malignancies continues to evolve.[150] Good responses of esophageal cancer to PDT have led to governmental approval of Photofrin® in several countries for either palliative use or treatment of inoperable or recurrent cancer in Canada. The use of PDT for early gastric cancer has great potential but several technical problems remain. PDT has proven generally effective for skin cancer when hematoporphyrin derivative or Photofrin® is used but more long-term follow-up data are required for PDT with 5-aminolevulinic acid.[164]

To date, the F.D.A. has approved Photofrin®, for use in PDT to treat or relieve the symptoms of esophageal cancer and non-small cell lung cancer. Porfimer sodium is approved to relieve symptoms of esophageal cancer when the cancer obstructs the esophagus or when the cancer cannot be satisfactorily treated with laser therapy alone. Porfimer sodium is also used to treat non-small cell lung cancer in patients for whom the usual treatments are not appropriate and to relieve symptoms in patients with non-small cell lung cancer that obstructs the airways. In 2003, the F.D.A. approved porfimer sodium for the treatment of precancerous lesions in patients with Barrett esophagus, a condition that can lead to esophageal cancer.[165-170]

Urology

Early studies on PDT with focal illumination for papillary bladder cancer obtained reasonable response rates for small tumors but recurrence was common. Whole bladder irradiation, once a suitable light-delivery system had been developed, gave promising outcomes with acceptable rates of complications.[164] In very early reports PDT was used as a diagnostic aid and therapy for superficial bladder cancer. [171]

PDT seems to be a promising nephron-sparing procedure but further investigations are needed to assess its efficiency. Photodynamic diagnosis has already been used to control surgical margins of partial nephrectomy with success showing the selective accumulation of protoporphyrin IX in renal clear cell carcinoma cells after photoactivation.[172,173] 5-aminolevulinic acid (Gliolan®) and its esters, methyl aminolevulinic acid (Metvix®) and hexaminolevulinic acid (Hexvix®) are used in topical application by cream for penile precancerous lesions detection and treatment and also by endovesical instillation for bladder superficial tumors detection and treatment.[172,174] Hypericine is effectively used for the treatment of bladder superficial tumors.[175]

Miscellaneous

Ovarian cancer can be treated using hexaminolevulinate.[176,177] PDT with porfimer sodium or verteporfin may be an effective means of purging bone marrow. The ability of malignant cells to selectively accumulate photosensitizing agents may account for efficacy of PDT in bone marrow purging.[178] PDT plus biliary stent placement may prolong survival (range of 360—630 days), reduce cholangitis, and improve the quality of life in patients with advanced disease.[179, 180] Use of hematoporphyrin monomethyl ether (HMME)-mediated vascular targeting PDT in the treatment of port wine stain (PWS) birthmarks is under clinical trials.[181, 182] The potential of HMME- PDT on viral and bacterial infections has also been reported.[183, 184] HMME might be useful in ocular PDT as well as anti-tumor PDT.[185, 186] PDT in conjunction with biliary stenting may improve bile duct patency by local obliteration of malignant tissue through the cytotoxic effects of reactive oxygen species. Stables *et al.* used PDT in order to treat 4 patients with erythroplasia of Queyrat using topical application of 5-ALA. One patient achieved a long-term complete response (36 months) and one recurred 18 months after an initial complete response. The 2 others had more extensive disease and only achieved significant improvement facilitating laser vaporization.[162] Clinical experience with PDT for gynecological cancer is limited and prospective studies are needed. In head and neck oncology, PDT should prove a useful option, but methodological problems need to be overcome.[164]

CONCLUSION

Though the history of phototherapy goes back to 3000 BC with the advent photodynamic reactions and photosensitizers in 1897, the ever growing hope of clinicians to treat and manage cancer with PDT is currently restricted due to the available but not so ideal photosensitizers and the limitations and unreliability with respect to dosimetry calculations. The need of the hour is more fruitful interdisciplinary research efforts between physical, biological, and medical sciences by the optical, medical and computational physicists, imaging scientists, cell biologists, medicinal chemists, clinicians and physicians that are focused on discovery of more selective and ideal photosensitizers, better understanding of mechanism of PDT, optical properties of various normal and tumorous tissues and targeted approach to make PDT more selective for the cancerous tissue and more safer for the cancer patients. Overall, PDT is now considered as an accepted treatment modality for various types of cancer than just a scientific curiosity or hypothetical approach with a definite possibility of finding further clinical applications in many non oncologic diseases.

REFERENCES

1. Dima, VF, Vasiliu V, Dima SV, Photodynamic therapy: An update, Roumanian Archives of Microbiology and Immunology, 57(3-4), 1998, 207-230.

2. Abrahamse H, Kresfelder T, Horne T, Cronje M, Nyokong T, Optical Methods for Tumor Treatment and Detection: Mechanisms and Techniques in Photodynamic Therapy XV. Kessel, D., Ed.; Proceedings of the SPIE, 6139, 2006, 17-28.

3. Abrahamse H, Photodynamic Cancer Therapy: Recent Advances, AIP Conf Proc 2011, Molecules, 16, 2011, 4140-4164.

4. Rao J, Photodynamic therapy for the dermatologist. http://emedicine.medscape.com/article/1121517 (accessed on 11th Jan, 2014).

5. www.macmillan.org.uk/Cancerinformation/Cancertreatment/Treatmenttypes/Othertreatments/Photodynamictherapy.aspx (accessed on 19th July, 2013).

6. El-Mofy AM, Vitiligo and Psoralens, Pergamon Press: Oxford, 1968.

7. Wyss P, Photomedicine in Gynecology and Reproduction. Wyss P, Tadir Y, Tromberg BJ, Haller U, Eds, Karger: Basel, 2000, 4-11.

8. Fahmy IR, Abu-Shady H, *Ammi majus* Linn: The isolation and properties of ammoidin, ammidin and majudin, and their effect in the treatment of leukoderma, Journal of Pharmacy and Pharmacology, 21, 1948, 499-503.

9. Celli JP, Spring BQ, Rizvi I, Evans CL, Samkoe KS, Verma S, Pogue BW, Hasan T, Imaging and photodynamic therapy: Mechanisms, monitoring, and optimization. Chemical Reviews, 110, 2010, 2795-2838.

10. Lipson RL, Baldes EJ, Hematoporphyrin derivative: A new aid for endoscopic detection of malignant disease, The Journal of Thoracic and Cardiovascular Surgery, 42, 1961, 623-629.

11. Dougherty TJ, Kaufman JE, Goldfarb A, Weishaupt KR, Boyle D, Mittleman, A, Photoradiation therapy for the treatment of malignant tumors, Cancer Research, 38, 1978, 2628-2635.

12. Kato H, Konaka C, Ono J, Kawate N, Nishimiya K, Shinohara H, Saito M, Sakai H, Noguchi M, Kito T, Preoperative laser photodynamic therapy in combination with operation in lung cancer. The Journal of Thoracic and Cardiovascular Surgery, 90, 1985, 420- 429.

International Journal of Pharmaceutical Sciences Review and Research
Available online at www.globalresearchonline.net
136

13. Moser JG, Definitions and general properties of 2nd and 3rd generation photosensitizers. In: Moser, J. G. (ed). Photodynamic tumor therapy-2nd and 3rd Generation photosensitizers, Harwood Academic Publishers; London, 1997, 3-8.

14. Mew D, Wat C, Towers G, Levy JC, Photo immunotherapy: Treatment of animal tumours with tumour-specific monoclonal antibody-hematoporphyrin conjugates, Journal of Immunology, 130, 1983, 1473-1477.

15. Stummer W, Reulen HJ, Novotny A, Stepp H, Tonn JC, Fluorescence-guided resections of malignant gliomas- An overview, Acta Neurochirurgica Supplement, 88, 2003, 9-12.

16. Biel MA, Photodynamic therapy and the treatment of head and neck neoplasia, Laryngoscope, 108, 1998, 1259-1268.

17. Huang ZA, Review of progress in clinical photodynamic therapy. Technology in Cancer Research and Treatment, 4(3), 2005, 283-293.

18. Nyman ES, Hynninen PH, Research advances in the use of tetrapyrrolic photosensitizers for photodynamic therapy, Journal of Photochemistry and Photobiology B: Biology, 73, 2004, 1-28.

19. Hasan T, Photodynamic Therapy: Basic principles and clinical applications; Dougherty, G. J, Henderson B. Eds.; Marcel Dekker: New York, 1992, 187-200.

20. Strong L, Yarmush DM, Yarmush ML, Antibody targeted photolysis: Photophysical, biochemical, and pharmacokinetic properties of antibacterial conjugates, Annals of the New York Academy of Sciences, 745, 1994, 297-320.

21. Kobayashi H, Ogawa M, Alford R, Choyke PL, Urano Y, New strategies for fluorescent probe design in medical diagnostic imaging, Chemical Reviews, 110, 2010, 2620-2640.

22. Shackley DC, Whitehurst C, Clarke NW, Betts C, Moore JV, Photodynamic therapy, Journal of the Royal Society of Medicine, 92, 1999, 562-565.

23. http://medicaldictionary.thefreedictionary.com/photosensitizer"> photosensitizer (accessed on 19th Jan 2014).

24. Allison RR, Downie GH, Cuenca R, Hu X, Childs CJH, Sibata CH, Photosensitizers in clinical PDT. Photodiagnosis and Photodynamic Therapy, 1, 2004, 27- 42.

25. Dougherty TJ, Pandey RK, Photosensitizing agents, US Patent 5,093, 1992, 349.

26. Allison RR, Sibata CH, Oncologic photodynamic therapy photosensitizers: A clinical review, Photodiagnosis and Photodynamic Therapy, 7, 2010, 61-75.

27. Leia TC, Glaznera GF, Duffy M, Scherrer L, Pendyala S, Li B, Wang X, Wang H, Huang Z, Optical properties of hematoporphyrin monomethyl ether (HMME), a PDT photosensitizer. Photo diagnosis and Photodynamic Therapy, 9, 2012, 232- 242.

28. Budzinskaia MV, Likhvantseva VG, Shevxchik SA, Loshchenov VB, Kuz'min SG, Vorozhtsov GN, Experimental assessment of the capacities of use of photosense. Communication 2. Photodynamic therapy for epibulbar and choroid tumors. Vestn. Oftalmol., 121(5), 2005, 17-19.

29. Milgrom LR, O'Neill F, Towards synthetic-porphyinymonoclonal antibody conjugates, Tetrahedron, 51, 1995, 2137-2144.

30. Allison BA, Pritchard PH, Levy JG, Evidence for low-density lipoprotein receptor-mediated uptake of benzoporphyrin derivative, British Journal of Cancer, 69, 1994, 833-839.

31. Bellnier DA, Greco WR, Loewen GM, Nava H, Oseroff AR, Dougherty TJ, Clinical pharmacokinetics of the PDT photosensitizers porfimer sodium (Photofrin), 2-[1-hexyloxyethyl]-2-devinyl pyropheophorbide-a (Photochlor) and 5-ALA-induced protoporphyrin IX. Lasers in Surgery and Medicine, 38(5), 2006, 439-444.

32. Kenney ME, Oleinick NL, Rihter BD, Phthalocyanine photosensitizers for photodynamic therapy, US5166197A, 1990.

33. Kato H, History of photodynamic therapy: Past, present and future, Gan to Kagaku Ryoho, 23(1), 1996, 8-15.

34. www.macmillan.org.uk/Cancerinformation/Cancertreatment/Trea tmenttypes/Othertreatments/Photodynamictherapy.aspx, (accessed on, 19th July, 2013)

35. Bellnier DA, Greco WR, Loewen GM, Nava H, Oseroff AR, Pandey RK, Tsuchida T, Dougherty TJ, Population pharmacokinetics of the photodynamic therapy agent 2-[1-hexyloxyethyl]-2-devinyl pyropheophorbide-a in cancer patients. Cancer Research, 63(8), 2003, 1806-1813.

36. http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/0204 51s019lbl.pdf (accessed on 1st Jan 2014)

37. http://journals.lww.com/jto/Fulltext/2006/06000/Photodynamic_ Therapy__PDT__for_Lung_Cancers.18.aspx "Photodynamic Therapy (PDT) for Lung Cancers" 2006 (accessed on 8th Dec 2013)

38. http://www.photofrin.com/healthcare-professional-home/mechanism-of-action/#sthash.W4QmhMJL.dpuf (accessed on 4th Feb 2014)

39. http://reference.medscape.com/drug/photofrin-porfimer-342226#10 (accessed on 4th Feb 2014)

40. http://www.accessdata.fda.gov/psn/printer-full.cfm?id=24 (accessed on 7th Feb 2014).

41. Kessel D, Photodynamic therapy: From the beginning, Photo diagnosis and Photodynamic Therapy, 1, 2004, 3-7.

42. Ackroyd R, Kelty C, Brown N, Reed M, The history of photo detection and photodynamic therapy, Journal of Photochemistry and Photobiology A, 74, 2001, 656-669.

43. Moan J, Peng Q, An outline of the hundred-year history of PDT, Anticancer Research, 23, 2003, 3591-3600.

44. Bonnett R, Photodynamic therapy in historical perspective. Rev. Contemp. Pharmacother, 10, 1999, 1-17.

45. Lorenz KJ, Maier H, Squamous cell carcinoma of the head and neck, Photodynamic therapy with Foscan. HNO, 56(4), 2008, 402-409.

46. O'Connor AE, Gallagher WM, Byrne AT, Porphyrin and nonporphyrin photosensitizers in oncology: Preclinical and clinical advances in photodynamic therapy, Journal of Photochemistry and Photobiology A, 85, 2009, 1053-1074.

47. http://www.highbeam.com/doc/1P2-18794532.html

Foscan approval saves Scotia's skin (accessed on 6th Feb 2014).

48. Brown SB, Vernon DI, Holroyd JA, Marcus S, Trust R, Hawkins W, Shah A, Tonelli A, Photodynamic Therapy and Biomedical Lasers, Spinelli P, Dal FM, Marchesini R, 1992, 475-479.

49. Jones HJ, Vernon DI, Brown SB, Photodynamic therapy effect of m-THPC (Foscans) in vivo: Correlation with pharmacokinetics, British Journal of Cancer, 89, 2003, 398- 404.

50. Marchal S, Fadloun A, Maugain E, D'Hallewin MA, Guillemin F, Bezdetnaya L, Necrotic and apoptotic features of cell death in response to Foscan® photo sensitization of HT29 monolayer and multicell spheroid, Biochemical Pharmacology, 69, 2005, 1167-1176.

51. Wagnieres G, Hadjur C, Grosjean P, Braichotte D, Savary JF, Monnier P, Van Den Bergh H, Clinical evaluation of the cutaneous photo toxicity of 5,10,15,20-tetra(m-hydroxyphenyl)chlorine, Journal of Photochemistry and Photobiology A, 68, 1998, 382-387.

52. Radu A, Zellweger M, Grosjean P, Monier P, Pulse oximeter as a cause of skin burn during photodynamic therapy. Endoscopy, 31, 1999, 831-833.

53. Schwarz VA, Klein SD, Hornung R, Knochenmuss R, Wyss P, Fink D, Haller U, Walt H, Skin protection for photosensitized patients, Lasers in Surgery and Medicine, 29, 2001, 252-259.

54. Allison RR, Cuenca R, Downie GH, Randall ME, Bagnato VS, Sibata CH, PD/PDT for gynecological disease: A clinical review, Photo diagnosis and Photodynamic Therapy, 2, 2005, 51-63.

55. Kübler AC, Photodynamic therapy. Med. Laser Appl., 20, 2005, 37-45.

56. Morton CA, Treating basal cell carcinoma: Has photodynamic therapy come of age? British Journal of Dermatology, 145, 2001, 1-2.

57. Gahlen J, Prosst R, Stern LJ, Photodynamische Therapie im Gastrointestinaltrakt. Möglichkeiten und Grenzen. Chirurg, 73, 2002, 122-131.

58. Mitton D, Ackroyd R, Photodynamic therapy in oesophageal carcinoma: An overview. Photochem. Photobiol. Sci, 3, 2004, 839-850.

59. Wolfsen, HC, Uses of photodynamic therapy in premalignant and malignant lesions of the gastrointestinal tract beyond the esophagus, Journal of Clinical Gastroenterology, 39, 2005, 653-664.

60. Wolfsen HC, Present status of photodynamic therapy for high-grade dysplasia in Barrett's esophagus. Journal of Clinical Gastroenterology, 2005, 39, 189-202.

61. Eljamel MS, Brain PDD and PDT unlocking the mystery of malignant gliomas. Photo diagnosis and Photodynamic Therapy, 1, 2004, 303-310.

62. Martin NE, Hahn SM, Interstitial photodynamic therapy for prostate cancer: A developing modality, Photo diagnosis and Photodynamic Therapy, 1, 2004, 123-136.

63. Eggener SE, Scardino PT, Carroll PR, Zelefsky MJ, Sartor O, Hricak H, Wheeler TM, Fine SW, J. M. A. Rubin, Ohori M, Kuroiwa K, Rossignol M, Abenhaim L, Focal therapy for localized prostate cancer: A critical appraisal of rationale and modalities, Journal of Urology, 178, 2007, 2260-2267.

64. Ahmed HU, Moore C, Emberton M, Minimally-invasive technologies in uro-oncology: The role of cryotherapy, HIFU and photodynamic therapy in whole gland and focal therapy of localised prostate cancer. Surg. Oncol., 18, 2009, 219-232.

65. Hillemanns P, Soergel P, Löning M, Fluorescence diagnosis and photodynamic therapy for lower genital tract diseases – A review, Med. Laser Appl, 24, 2009, 10-17.

66. Ayaru L, Bown SG, Pereira SP, Photodynamic therapy for pancreatic carcinoma: Experimental and clinical studies, Photodiagnosis and Photodynamic Therapy, 1, 2004, 145-155.

67. Allison RR, Sibata CT, Mang S, Bagnato VS, Downie GH, Hu XH, Cuenca R, Photodynamic therapy for chest wall recurrence from breast cancer. Photo diagnosis and Photodynamic Therapy, 1, 2004, 157-171.

68. Pinthus JH, Bogaards A, Weersink R, Wilson BC, Trachtenberg J, Photodynamic therapy for urological malignancies: Past to current approaches, Journal of Urology, 175(4), 2006, 1201-1207.

69. Grosjean P, Wagnieres G, Fontolliet, van den Bergh H, Monnier P, Clinical photodynamic therapy for superficial cancer in the oesophagus and the bronchi: 514nm compared with 630 nm light irradiation after sensitization with Photofrin II, British Journal of Cancer, 1998, 77(11), 1989-1995.

70. Grosjean P, Savary JF, Mizeret J, Wagnières G, Woodtli A, Theumann JF, Fontolliet C, van den Bergh H, Monnier P, Photodynamic therapy for cancer of the upper aero digestive tract using tetra(m-hydroxyphenyl)chlorine, Journal of Clinical Laser Medicine and Surgery, 14(5), 1996, 281-287.

71. Friedberg JS, Mick R, Stevenson J, Metz J, Zhu T, Buyske J, Sterman DH, Pass HI, Glatstein E, Hahn SM, A phase I study of Foscan-mediated photodynamic therapy and surgery in patients with mesothelioma, The Annals of Thoracic Surgery, 75(3), 2003, 952-959.

72. Schouwink H, Rutgers ET, van der Sijp J, Oppelaar H, van Zandwijk, van Veen R, Burgers S, Stewart FA, Zoetmulder F, Baas P, Intraoperative photodynamic therapy after pleuropneumonectomy in patients with malignant pleural mesothelioma: Dose finding and toxicity results, Chest, 120(4), 2001, 1167-1174.

73. Ris HB, Altermatt HJ, Nachbur B, Stewart CM, Wang Q, Lim CK, Bonnett R, Althaus U, Intraoperative photodynamic therapy with m-tetrahydroxyphenylchlorin for chest malignancies, Lasers in Surgery and Medicine., 1996, 18(1), 39-45.

74. Savary JF, Monnier P, Fontolliet C, Mizeret, J, Wagnières, G, Braichotte D, van den Bergh HP, Photodynamic therapy for early squamous cell carcinomas of the esophagus, bronchi, and mouth with m-tetra (hydroxyphenyl) chlorin. Archives of Otolaryngology-Head and Neck Surgery, 123(2), 1997, 162-168.

75. Kubin A, Wierrani F, Burner U, Alth G, Grünberger W, Hypericin-the facts about a controversial agent, Current Pharmaceutical Design, 11(2), 2005, 233-253.

76. Agostinis P, Vantieghem A, Merievede W, de Witte PA, Hypericin in cancer treatment: more light on the way, International Journal of Biochemistry and Cell Biology, 34, 2002, 221-241.

77. Schey KL, Patat S, Chignell CF, Datillo M, Wang RH, Roberts JE, Photo-oxidation of lens alpha-crystalline by hypericin (active ingredient in St. John's Wort), Journal of Photochemistry and Photobiology A, 72(2), 2000, 200-203.

78. Diwu Z, Novel therapeutic and diagnostic applications of hypocrellins and hypericins, Journal of Photochemistry and Photobiology A, 61(6), 1995, 529-539.

79. Duran N, Song P, Hypericin and its photodynamic action. Journal of Photochemistry and Photobiology A, 43, 1986, 677-680.

80. Walker LW, A review of the hypothetical biogenesis and regulation of hypericin synthesis via the polyketide pathway in Hypericum perforatum and experimental methods proposed to evaluate the hypothesis 1999, http://www.l2w.cc/pages/HYPE/ Master's thesis. Portland State University.

81. Duráan N, Song P, Hypericin and its photodynamic action. Journal of Photochemistry and Photobiology A, 43(6), 1986, 677-680.

82. Yavari N, Andersson-Engels S, Segersten U, Malmstrom PU, An overview on preclinical and clinical experiences with photodynamic therapy for bladder cancer, Canadian Journal of Urology, 18(4), 2011, 5343-5351.

83. Oubre A, Hypericin: The active ingredient in Saint John's Wort. 1991, http://web.archive.org/web/20070928004046/http://www.delano.com/ReferenceArticles/Hypericin-Active.html.

84. Levy JG, Waterfield E. Richter AM, Smits C, Salvatori V, Photodynamic therapy of malignancies with benzoporphyrin derivative monoacid ring A, Proceedings of the Society of Photo-Optical Instrumentation Engineers, 2078, 1994, 99-101.

85. Houle JM, Strong A, Clinical pharmacokinetics of verteporfin, Journal of Clinical Pharmacology, 42(5), 2002, 547-557.

86. Houle JM, Strong HA, Duration of skin photosensitivity and incidence of photosensitivity reactions after administration of verteporfin. Retina, 22(6), 2002, 691-697.

87. Leung J, Photosensitizers in photodynamic therapy. Seminars in Oncology, 21, 1994, 4-10.

88. Richter AM, Kelly B, Chow J, Liu DJ, Towers GH, Dolphin D, Levy JG, Preliminary studies on a more effective phototoxic agent than hematoporphyrin. J. Natl. Cancer Inst., 1987, 79(6), 1327-1332.

89. Gragoudas E, Schmidt-Erfurth U, Sickenkey M, Results and preliminary dosimetry of photodynamic therapy for choroidal neovascularization in age-related macular degeneration in a phase I/II study, Association For Research In Vision And Ophthalmology, 38, 1997, 73-76.

90. Blinder KJ, Blumenkranz MS, Bressler NM, Bressler SB, Donato G, Lewis H, Lim JI, Menchini, U, Miller JW, Mones JM, Potter MJ, Pournaras C, Reaves A, Rosenfeld P, Schachat AP, Schmidt-Erfurth U, Sickenberg M, Singerman LJ, Slakter JS, Strong HA, Virgili G, Williams GA, Verteporfin therapy of subfoveal choroidal neovascularization in pathologic myopia: 2-year results of a randomized clinical trial—VIP report no. 3. Ophthalmology, 110(4), 2003, 667-673.

91. Young LH, Howard MA, Hu LK, Kim RY, Gragoudas ES, Photodynamic therapy of pigmented choroidal melanomas using a liposomal preparation of benzoporphyrin derivative. Archives of Ophthalmology, 14(2), 1996, 186-192.

92. Barbazetto IA, Lee TC, Rollins IS, Chang S, Abramson DH. Treatment of choroidal melanoma using photodynamic therapy, American Journal of Ophthalmology, 135(6), 2003, 898-899.

93. Lui, H. Photodynamic therapy in dermatology with porfimer sodium and benzoporphyrin derivative: an update. Seminars in Oncology, 21(6 Suppl 15), 1994, 11-14.

94. Pandey RK, Bellnier DA, Smith KM, Dougherty TJ, Chlorin and porphyrin derivatives as potential photosensitizers in photodynamic therapy. Journal of Photochemistry and Photobiology A, 53(1), 1991, 65-72.

95. Magne ML, Rodriguez CO, Autry SA, Edwards BF, Theon AP, Madewell BR, Photodynamic therapy of facial squamous cell carcinoma in cats using a new photosensitizer, Lasers in Surgery and Medicine, 20(2), 1997, 202-209.

96. McCaw DL, Pope ER, Payne JT, West MK, Tompson RV, Tate D, Treatment of canine oral squamous cell carcinomas with photodynamic therapy, British Journal of Cancer, 82(7), 2000, 1297-1299.

97. Bellnier DA, Greco WR, Loewen GM, Nava H, Oseroff AR, Pandey RK, Tsuchida T, Dougherty TJ, Population pharmacokinetics of the photodynamic therapy agent 2- [1-hexyloxyethyl]-2-devinyl pyropheophorbide-a in cancer patients, Cancer Research, 63(8), 2003, 1806-1813.

98. Young SW, Woodburn KW, Wright M, Mody, TD, Fan Q, Sessler JL, Dow WC, Miller RA, Lutetium texaphyrin (PCI-0123): a near-infrared, water-soluble photosensitizer, Journal of Photochemistry and Photobiology A, 63(6), 1996, 892-897.

99. Sessler JL, Miller RA, Texaphyrins: new drugs with diverse clinical applications in radiation and photodynamic therapy, Biochemical Pharmacology, 59(7), 2000, 733-739.

100. Sessler JL, Hemmi G, Mody TD, Murai T, Burrell A, Young SW, Texaphyrins: synthesis and applications, Accounts of Chemical Research, 27, 1994, 43-50.

101. Carde P, Timmerman R, Mehta MP, Koprowski CD, Ford J, Tishler RB, Miles D, Miller RA, Renschler MF, Multicenter phase Ib/II trial of the radiation enhancer motexafin gadolinium in patients with brain metastases, Journal of Clinical Oncology, 19(7), 2001, 2074-2083.

102. Dimofte A, Zhu TC, Hahn SM, Lustig RA, In vivo light dosimetry for motexafin lutetium-mediated PDT of recurrent breast cancer. Lasers in Surgery and Medicine, 31(5), 2002, 305-312.

103. Peng Q, Berg K, Moan J, Kongshaug M, Nesland JM, 5-Aminolevulinic acid-based photodynamic therapy: Principles and experimental research, Journal of Photochemistry and Photobiology A, 65, 1997, 235-251.

104. Ben-Hur E, Rosenthal I, The phthalocyanines: A new class of mammalian cell photosensitizers with a potential for cancer phototherapy, International Journal of Radiation Biology, 47, 1985, 145-147.

105. Bonnett R, Photosensitizers of the porphyrin and phthalocyanine photodynamic therapy, Chemical Society Reviews, 24, 1995, 19-33.

106. Stradnadko EF, Skobelkin OK, Vorozhtsov GN, Photodynamic therapy of cancer: five year clinical experience, Proceedings of the Society of Photo-Optical Instrumentation Engineers, 3191, 1997, 253- 262.

107. Ben-Hur E, Rosenthal I, The phthalocyanines: A new class of mammalian cells photosensitizers with a potential for cancer phototherapy, International Journal of Radiation Biology & Related Studies in Physics, Chemistry & Medicine, 47(2), 1985, 145-147.

108. Allen CM, Sharman WM, Van Lier JE. Current Status of phthalocyanines in the photodynamic therapy of cancer, Journal of porphyrins and phthalocyanines, 5, 2001, 161-169.

109. Abernathy CD, Anderson RE, Kooistra KL, Laws ER, Activity of phthalocyanine photosensitizers against human glioblastoma in vitro, Neurosurgery, 21(4), 1987, 468-473.

110. Chan WS, Marshall JF, Lam GY, Hart IR, Tissue uptake, distribution, and potency of the photo activatable dye chloroaluminum sulfonated phthalocyanine in mice bearing transplantable tumors, Cancer Research, 48, 1988, 3040-3044.

111. Sonoda M, Krishna CM, Riesz P, The role of singlet oxygen in the photohemolysis of red blood cells sensitized by phthalocyanine sulfonates, Journal of Photochemistry and Photobiology A, 46, 1987, 625-632.

112. Berg K, Bommer JC, Moan J, Evaluation of sulfonated aluminum phthalocyanines for use in photo chemotherapy. cellular uptake studies, Cancer Letters, 44, 1989, 7-15.

113. Rosenthal I, Ben-Hur E, Greenberg S, Concepcion-Lam A, Drew DM, Leznoff CC, The effect of substituent's on phthalocyanine photo toxicity, Journal of Photochemistry and Photobiology A, 46, 1987, 959-963.

114. Uspenskiǐ LV, Chistov LV, Kogan EA, Loshchenov VB, Ablitsov A, Rybin VK, Zavodnov V I, Shiktorov DI, Serbinenko NF, Semenova IG, Endobronchial laser therapy in complex preoperative preparation of patients with lung diseases. Khirurgiia (Mosk), 2, 2000, 38-40.

115. Sokolov VV, Stranadko EF, Zharkova NN, Iakubovskaia RI, Filonenko EV, The photodynamic therapy of malignant tumors in basic sites with the preparations photohem and photosens (the results of 3 years of observations), Voprosy onkologii, 41(2), 1995, 134-138.

116. Stranadko EF, Garbuzov MI, Zenger VG, Nasedkin AN, Photodynamic therapy of recurrent and residual oropharyngeal and laryngeal tumors, Vestn Otorinolaringol, 3, 2001, 36-39.

117. Ackroyd R, Brown N, Vernon D, Roberts D, Stephenson T, Marcus S, Stoddard C, Reed M, 5-Aminolevulinic acid photosensitization of dysplastic Barrett's esophagus: A pharmacokinetic study. Journal of Photochemistry and Photobiology A, 70, 1999, 656-666.

118. Bonnett R, Photosensitizers of the porphyrin and phthalocyanine series for photodynamic therapy, Chemical Society Reviews, 24, 1995, 19-33.

119. Milgrom L, MacRobert S, Light years ahead, European Journal of Inorganic Chemistry, 34, 1998, 45-50.

120. Peng Q, Warloe T, Berg K, Moan J, Kongshaug M, Giercksky KE, Nesland JM, 5-Aminolevulinic acid-based photodynamic therapy—clinical research and future challenges, Cancer, 79, 1997, 2282-2308.

121. Collaud S, Juzeniene A, Moan J, Lange N, On the selectivity of 5-aminolevulinic acid-induced protoporphyrin IX formation, Anti-Cancer Agents in Medicinal Chemistry, 4, 2004, 301-316.

122. Profio AE, Doiron DR, Dosimetry considerations in phototherapy, Medical Physics, 8, 1981, 190-196.

123. Dalton JT, Yates CR, Yin D, Straughn A, Marcus SL, Golub AL, Meyer MC, Clinical pharmacokinetics of 5-aminolevulinic acidin healthy volunteers and patients at high risk for recurrent bladder cancer. Journal of Pharmacology and Experimental Therapeutics, 301, 2002, 507-512.

124. Loh CS, MacRobert AJ, Bedwell J, Regula J, Krasner N, Bown SG, Oral versus intravenous administration of 5-aminolaevulinic acid for photodynamic therapy, British Journal of Cancer, 68, 1993, 41-51.

125. Warren CB, Karai LJ, Vidimos A, Maytin EV, Pain associated with aminolevulinic acid-photodynamic therapy of skin disease, Journal of the American Academy of Dermatology, 61, 2009, 1033-1043.

126. Christensen E, Warloe T, Kroon S, Funk J, Helsing P, Soler AM, Stang HJ, Vatne O, Mork C, Guidelines for practical use of MAL-PDT in non-melanoma skin cancer, Journal of the European Academy of Dermatology and Venereology, 24, 2010, 505-512.

127. Makowski M, Grzela T, Niderla JM, Mroz P, Kopee M, Legat M, Strusinska K, Koziak K, Nowis D, Mrowka P, Wasik M, Jakobisiak M, Golab J, Inhibition of cyclooxygenase-2 indirectly potentiates antitumor effects of photodynamic therapy in mice, Clinical Cancer Research, 9, 2003, 5417-5422.

128. Siddiqui MA, Perry CM, Scott LJ, Topical methyl aminolevulinate. American Journal of Clinical Dermatology, 5(2), 2004, 127-137.

129. Smits T, Moor AC, New aspects in photodynamic therapy of actinic keratoses, Journal of Photochemistry and Photobiology B, 96(3), 2009, 159-169.

130. www.drugs.com/mtm/methyl-aminolevulinate-topical.html (accessed on 12th Feb 2014)

131. Fotinos N, Campo MA, Popowycz F, Gurny R, Lange N, 5-Aminolevulinic acid derivatives in photo medicine: characteristics, application and perspectives, Journal of Photochemistry and Photobiology A, 82(4), 2006, 994-1015.

132. www.drugs.com/cysview.htm (accessed on 14th Feb 2014)

133. www.accessdata.fda.gov/drugsatfda_docs/label/.../022555s000lbl.pdf (accessed on 20th Feb 2014)

134. http://cysview.net/medical-journalists/press-release.html (accessed on 20th Feb 2014)

135. http://reference.medscape.com/drug/cysview-hexaminolevulinate-999579#10 Page (accessed on 20th Feb 2014)

136. Levy JG, Photosensitizers in photodynamic therapy, Seminars in Oncology, 21(6 Suppl 15), 1994, 4-10.

137. Fish AM, Murphree AL, Gomer CJ, Clinical and preclinical photodynamic therapy, Lasers in Surgery and Medicine, 17(1), 1995, 2-31.

138. Park S, Delivery of photosensitizers for photodynamic therapy, Korean Journal of Gastroenterology, 49(5), 2007, 300-313.

139. Selbo PK, Hogset A, Prasmickaite L, Berg K, Photochemical internalisation: a novel drug delivery system, Tumour Biology, 23(2), 2002, 103-112.

140. Silva JN, Filipe P, Morliere P, Maziere JC, Freitas JP, Cirne de Castro JL, Santus R, Photodynamic therapies: principles and present medical applications. Journal of Biomedical Materials Research, 16(4 Suppl), 2006, S147-154.

141. Chen B, Pogue BW, Hoopes PJ, Hasan T, Vascular and cellular targeting for photodynamic therapy, Critical Reviews in Eukaryotic Gene Expression, 2006, 16(4), 279–305.

142. Krammer B, Vascular effects of photodynamic therapy, Anticancer Research, 21(6B), 2001, 4271-4277.

143. Bissonette R, Bergeron A, Liu Y, Large surface photodynamic therapy with aminolevulinic acid: Treatment of actinic keratoses and beyond, Journal of Drugs in Dermatology, 3(1 Suppl), 2004, S26-31.

144. Jeffes EW, McCullough JL, Weinstein GD, Fergin PE, Nelson JS, Shull TF, Simpson KR, Bukaty LM, Hoffman WL, Fong NL, Photodynamic therapy of actinic keratosis with topical 5-aminolevulinic acid. A pilot dose-ranging study, Archives of Dermatological Research, 133(6), 1997, 727-732.

145. Jeffes EW, McCullough JL, Weinstein GD, Kaplan R, Glazer SD, Taylor JR, Photodynamic therapy of actinic keratoses with topical aminolevulinic acid hydrochloride and fluorescent blue light, Journal of the American Academy of Dermatology, 45(1), 2001, 96-104.

146. Kurwa HA, Yong-Gee SA, Seed PT, Markey AC, Barlow RJ, A randomized paired comparison of photodynamic therapy and topical 5-fluorouracil in the treatment of actinic keratoses, Journal of the American Academy of Dermatology, 41(3 Pt 1), 1999, 414-418.

147. Pariser DM, Lowe NJ, Stewart DM, Jarratt MT, Lucky AW, Pariser RJ, Yamauchi PS, Photodynamic therapy with topical methyl aminolevulinate for actinic keratosis: Results of a prospective randomized multicenter trial, Journal of the American Academy of Dermatology, 48(2), 2003, 227-232.

148. Piacquadio DJ, Chen DM, Farber HF, Fowler JF Jr, Glazer SD, Goodman JJ, Hruza LL, Jeffes EW, Ling MR, Phillips TJ, Rallis TM, Scher RK, Taylor CR, Weinstein GD, Photodynamic therapy with aminolevulinic acid topical solution and visible blue light in the treatment of multiple actinic keratoses of the face and scalp: investigator-blinded, phase 3, multicenter trials, Archives of Dermatology research, 140(1), 2004, 41-46.

149. Touma D, Yaar M, Whitehead S, Konnikov N, Gilchrest BA A trial of short incubation, broad-area photodynamic therapy for facial actinic keratoses and diffuse photodamage, Archives of Dermatology Research, 140(1), 2004, 33-40.

150. Telfer NR, Colver GB, Morton CA, Guidelines for the management of basal cell carcinoma, British Journal of Dermatology., 159(1), 2008, 35-48.

151. www.dermnetnz.org/procedures/metvix-pdt.html "Methyl aminolevulinate photodynamic therapy (MAL PDT)" (accessed on 14th Jan 2014)

152. Hongcharu W, Taylor CR, Chang, Y, Aghassi D, Suthamjariya K, Anderson RR, Topical ALA photodynamic therapy for the treatment of acne vulgaris, Journal of Investigative Dermatology, 115(2), 2000, 1183-1192.

153. Itoh Y, Ninomiya Y, Tajima S, Ishibashi A, Photodynamic therapy for acne vulgaris with topical 5-aminolevulinic acid, Archives of Dermatology research, 136(9), 2000, 1093-1095.

154. Itoh Y, Ninomiya Y, Tajima S, Ishibashi A, Photodynamic therapy of acne vulgaris with topical deltaaminolaevulinic acid and incoherent light in Japanese patients. British Journal of Dermatology, 144(3), 2001, 575-579.

155. Santos, M. A.; Belo, V. G.; Santos, G. Effectiveness of photodynamic therapy with topical 5-aminolevulinic acid and intense pulsed light versus intense pulsed light alone in the treatment of acne vulgaris: Comparative study, Dermatologic Surgery, 2005, 31(8 Pt 1), 910-915.

156. Silver H, Psorisis vulgaris treated with hematoporphyrin, Archives of Dermatology and Syphilology, 1937, 118-119.

157. NCT00706433 Light dose ranging study of photodynamic therapy (PDT) with Levulan + blue light versus vehicle + blue light in severe facial acne, http://ichgcp.net/clinical-

trialsregistry/research/find?intr=Light%2BTherapy&page=4 (accessed on 17th Dec 2013)

158. Jones CM, Mang T, Cooper M, Wilson BD, Stoll HL, Jr. Photodynamic therapy in the treatment of Bowen's disease, Journal of the American Academy of Dermatology, 27(6 Pt 1), 1992, 979-982.

159. Morton CA, Whitehurst C, Moseley H, McColl JH, Moore JV, Mackie RM, Comparison of photodynamic therapy with cryotherapy in the treatment of Bowen's disease, British Journal of Dermatology, 135(5), 1996, 766-771.

160. Morton CA, Whitehurst C, McColl JH, Moore JV, MacKie RM, Photodynamic therapy for large or multiple patches of Bowen disease and basal cell carcinoma, Archives of Dermatology research, 137(3), 2001, 319-324.

161. Robinson PJ, Carruth JA, Fairris GM, Photodynamic therapy: a better treatment for widespread Bowen's disease, British Journal of Dermatology, 119(1), 1988, 59-61.

162. Stables GI, Stringer MR, Robinson DJ, Ash DV, Large patches of Bowen's disease treated by topical aminolaevulinic acid photodynamic therapy, British Journal of Dermatology, 136(6), 1997, 957-960.

163. Marcon NE, Photodynamic therapy and cancer of the esophagus, Seminars in Oncology, 21(6 Suppl 15), 1994, 20-23.

164. Chang SC, Bown SG, Photodynamic therapy: applications in bladder cancer and other malignancies, Journal of the Formosan Medical Association, 96(11), 1997, 853-863.

165. Dolmans DE, Fukumura D, Jain RK, Photodynamic therapy for cancer, Nature Review Cancer, 3(5), 2003, 380-387.

166. Wilson BC, Photodynamic therapy for cancer: principles. Canadian Journal of Gastroenterology & Hepatology, 16(6), 2002, 393-396.

167. Vrouenraets MB, Visser GW, Snow GB, van Dongen GA, Basic principles, applications in oncology and improved selectivity of photodynamic therapy, Anticancer Research, 23(1B), 2003, 505-522.

168. Dougherty TJ, Gomer CJ, Henderson BW, Jori G, Kessel D, Korbelik M, Moan J, Peng Q, Photodynamic therapy, Journal of the National Cancer Institute, 90(12), 1998, 889-905.

169. Gudgin Dickson EF, Goyan RL, Pottier RH, New directions in photodynamic therapy, Cell and Molecular Biology, 48(8), 2002, 939-954.

170. Capella MA, Capella LS, A light in multidrug resistance: photodynamic treatment of multidrug-resistant tumors, Journal of Biomedical Science, 10(4), 2003, 361-366.

171. Kelly JF, Snell ME, Hematoporphyrin derivative: a possible aid in the diagnosis and therapy of carcinoma of the bladder, Journal of Urology, 115(2), 1976, 150-151.

172. Bozzini G, Colina P, Betrouni N, Nevouxa P, Ouzzanea A, Puechd P, Villers A, Mordon S, Photodynamic therapy in urology: What can we do now and where are we heading Photodiagnostics and Photodynamic therapy, 9(3), 2012, 261-273.

173. Popken G, Wetterauer U, Schultze-Seemann W, Kidney preserving tumour resection in renal cell carcinoma with photodynamic detection by 5-aminolaevulinic acid: Preclinical and preliminary clinical results, BJU International, 83(6), 1999, 578-582.

174. Fotinos N, Campo MA, Popowycz F, Gurny R, Lange, N, 5-Aminolevulinic acid derivatives in photomedicine: Characteristics, application and perspectives, Journal of Photochemistry and Photobiology A, 82(4), 2006, 994-1015.

175. Kamuhabwa A, Agostinis P, Ahmed B, Landuyt W, van Cleynenbreugel B, van Poppel H, De Witte P, Hypericin as a potential phototherapeutic agent in superficial transitional cell carcinoma of the bladder, Journal of Photochemistry and Photobiology B, 3(8), 2004, 772-780.

176. Tyrrell JS, Campbell SM, Curnow A, The relationship between protoporphyrin IX photobleaching during real-time dermatological methyl-aminolevulinate photodynamic therapy (MAL-PDT) and subsequent clinical outcome, Lasers in Surgery and Medicine., 42(7), 2010, 613-619.

177. Ascencio M, Collinet P, Farine MO, Mordon S, Protoporphyrin IX fluorescence photobleaching is a useful tool to predict the response of rat ovarian cancer following hexaminolevulinate photodynamic therapy, Lasers in Surgery and Medicine, 40(5), 2008, 332-341.

178. Mulroney CM, Glück S, Ho AD, The use of photodynamic therapy in bone marrow purging, Seminars in Oncology., 21(6 Suppl 15), 1994, 24-27.

179. Ortner ME, Caca K, Berr F, Liebetruth J, Mansmann U, Huster D, Voderholzer W, Schachschal G, Mössner J, Lochs H, Successful photodynamic therapy for nonresectable cholangiocarcinoma: A randomized prospective study, Journal of Gastroenterology, 125, 2003, 1355-1363.

180. Matull WR, Dhar DK, Ayaru L, Sandanayake NS, Chapman MH, Dias A, Bridgewater J, Webster GJ, Bong JJ, Davidson BR, Pereira SP, R0 but not R1/R2 resection is associated with better survival than palliative photodynamic therapy in biliary tract cancer, Liver International, 31, 2011, 99-107.

181. Yuan KH, Li Q, Yu WL, Zeng D, Zhang C, Huang Z, Comparison of photodynamic therapy and pulsed dye laser in patients with port wine stain birthmarks: A retrospective analysis. Photo diagnosis and Photodynamic Therapy, 5, 2008, 50-57.

182. Huang Z, An update on the regulatory status of PDT photosensitizers in China. Photo diagnosis and Photodynamic Therapy, 5, 2008, 285-287.

183. Yin H, Li Y, Zou Z, Qiao W, Yao X, Su Y, Inactivation of bovine immunodeficiency virus by photodynamic therapy with HMME. Chinese Optics Letters, 6, 2008, 944-946.

184. Zou Z, Gao P, Yin H, Li YY, Investigation of photodynamic therapy streptococcus mutants of oral biofilm, Chinese Optics Letters, 6, 2008, 947-949.

185. Fan SJ, Gu Y, Qiu HX, Zeng J, Huang HB, Effects of photodynamic therapy using hematoporphyrin monomethyl ether on experimental choroidal neovascularisation, Journal of Clinical Laser Medicine & Surgery, 17, 2008, 80-85.

186. Song K, Kong B, Li L, Yang Q, Wei Y, Qu X, Intraperitonial photodynamic therapy for an ovarian cancer ascite model in Fischer 344 rat using hematoporphyrin monomethyl ether, Cancer Science, 98, 2007, 1959-1964.

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