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Photodynamic therapy: a new concept in medical treatment

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Abstract

A new concept in the therapy of both neoplastic and non-neoplastic diseases is discussed in this article. Photodynamic therapy (PDT) involves light activation, in the presence of molecular oxygen, of certain dyes that are taken up by the target tissue. These dyes are termed photosensitizers. The mechanism of interaction of the photosensitizers and light is discussed, along with the effects produced in the target tissue. The present status of clinical PDT is discussed along with the newer photosensitizers being used and their clinical roles. Despite the promising results from earlier clinical trials of PDT, considerable additional work is needed to bring this new modality of treatment into modern clinical practice. Improvements in the area of light source delivery, light dosimetry and the computation of models of treatment are necessary to standardize treatments and ensure proper treatment delivery. Finally, quality assurance issues in the treatment process should be introduced.

Key words
- Photodynamic therapy (PDT)
- Light delivery
- Clinical PDT
- State of art of PDT

Introduction

Photodynamic therapy (PDT) is a relatively new therapeutic modality for both neoplastic and non-neoplastic diseases, which involves light activation, in the presence of molecular oxygen, of certain dyes (photosensitizers) that have been somewhat selectively taken up by the target tissue. Photosensitizers are compounds that absorb energy from light of specific wavelengths and are capable of using that energy to induce reactions in other non-absorbing molecules. Therefore, all three components (photosensitizer, light and oxygen) have to be available for the treatment to occur.

The concept of PDT began with studies by Oscar Raab in 1900 on the effects of light and dyes on Paramecia (1). The modern era of PDT began with studies by Lipson and Schwartz at the Mayo Clinic in 1960, who observed that injection of crude preparations of hematoporphyrin led to fluorescence of neoplastic lesions that could be visualized during surgery. Since then, considerable work has been done on how the process works, how to maximize efficacy using animal models, and how to best treat human tumors (2). These pre-clinical and clinical studies recently resulted in the approval of the first photosensitizing drug (Photofrin®) for the treatment of selected tumors (3). Photofrin® is a mixture of porphyrin oligomers (QLT Phototherapeutics Inc., Vancouver, BC, Canada). Since Photofrin® clears from normal skin and muscle tissues faster than from superficial tumor tissue, it has been found that differential damage to the tumor as compared to normal tissues can be optimized by applying the light 48 h after an intravenous

injection of Photofrin® (4). Photofrin® has been approved in Canada for the prophylactic treatment of bladder cancer, and The Netherlands, France, Germany, and Japan have approved it in patients with early and advanced stage cancer of the lung, digestive tract, and genitourinary tract (3). In the US, Photofrin® is the only photosensitizer approved by the FDA for clinical use for "palliation of patients with completely obstructing esophageal cancer, or of patients with partially obstructing esophageal cancer who, in the opinion of their physician, cannot be satisfactorily treated with Nd:YAG laser therapy, and for treatment of microinvasive endobronchial non-small cell lung cancer in patients for whom surgery and radiotherapy are not indicated" (1,5). The FDA approval includes the uses of a sterile microlens and cylinder-diffusing fibers (1, 1.5, 2.0, 5.0 cm).

Several second-generation photosensitizers are being investigated for treatment of a variety of tumors (3,6), but also in non-cancer applications, including ophthalmology (7), dermatology (6), cardiology (8), virus inactivation (9), and blood purification (10). These photosensitizers have been designed to improve the selectivity of uptake and to take advantage of the greater depth of penetration of light of longer wavelengths than that used to activate Photofrin®. Clinical trials are being conducted with these photosensitizers at many centers around the world in an effort to provide information for drug approval (3,6-8,10,11).

Ideally, the photosensitizer should be retained selectively in the tumor; in practice normal tissues, especially skin, also retain the photosensitizer, and the patient's skin can become sensitive to light exposure (including sunlight) for a period of weeks. Due to the variable tumor selectivity of the photosensitizers, it is necessary to optimize the distribution of the delivered light to coincide with the geometric and optical characteristics of the targeted tumor tissue, thereby minimizing damage to surrounding normal tissues. A variety of light sources can be used, provided that the intensity is high enough and the wavelength is within the appropriate range (12). Today, the use of lasers to activate photosensitizers has become synonymous with PDT. In fact, for treatment of many tumor sites, e.g., in the esophagus and the bronchus, only lasers produce sufficient power to permit coupling to a fiber optic system and delivery of light to the appropriate site with minimal energy loss. The photosensitizer dose (mg/kg of body weight), time window for treatment (hours or days after injection of photosensitizer) and energy density (fluence) depend on the balance between concentration of the drug in the tumor (target) tissue (mg/g tissue) and in normal tissues at the time of light irradiation. The choices of these parameters have typically been based on drug pharmacokinetics and pre-clinical trials done in experimental animals. This paper will present an overview of the therapeutic applications of PDT for neoplastic and non-neoplastic diseases.

Mechanisms of photodynamic therapy

The process is initiated when the photosensitizer absorbs a photon and undergoes simultaneous or sequential decays that result in intramolecular energy transfer reactions. The main classes of reactions are photooxidation by radicals (type I reaction), photooxidation by singlet oxygen (type II reaction), and photoreaction not involving oxygen (type III reaction) (13). These processes can occur simultaneously or in competition as detailed in Figure 1. Briefly, after the photosensitizer absorbs light, it is activated to an excited singlet state. Molecules at this state readily decay back to the ground state with the emission of light (fluorescence) or heat, or they can cross to the triplet state. In addition, molecules in the excited singlet state can undergo type I and III reactions.

The photosensitizer in the triplet state can react with ground-state oxygen to produce a singlet-state oxygen (type II reaction), decay to the ground state by phosphorescence, or undergo type I and III reactions. Singlet oxygen (a non-radical but highly reactive form of oxygen) is generally accepted as the major damaging species in PDT (14). Other reactive oxygen species may also be involved in the tumor ablation caused by PDT (11).

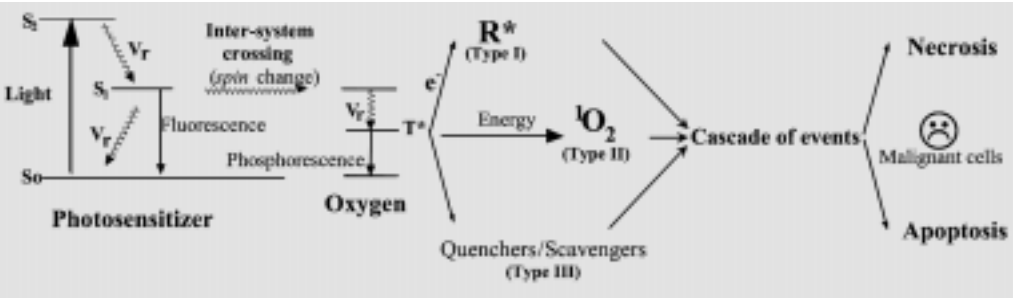
The complex nature of the tumor response to PDT has yet to be fully elucidated. PDT depends on the photodynamic events in malignant cells or within cells of the tumor vasculature. In the latter case, damage to the tumor vasculature can result in profound effects, including blood flow stasis, vascular collapse, and/or vascular leakage (15,16). Damage either to the malignant cells or to cells of the vasculature results in the death of tumor cells. PDT has been shown to induce apoptosis (a programmed process of cell death that is responsible for the orderly elimination of cells during normal tissue development) in many cells *in vitro*, and in all animal tumors tested *in vivo*. Apoptosis in response to toxic agents proceeds from the signaling of cell stress and culminates in the activation of a cascade of cysteine proteases, termed caspases, that catalyze the final degradation of key cellular proteins, including the nuclear protein poly(ADP-ribose) polymerase (11,17,18). In animal systems, gross edema and erythema are the first clinical signs of PDT response.

Light interaction with tissue

In principle, the basic phenomena occurring when matter is exposed to light are the following:

- reflection and refraction
- absorption
- scattering

Reflection and refraction are closely related. Refraction is accounted for by a displacement of the transmitted beam through the medium. Refraction plays a role in the optics of the instrumentation used to apply light for PDT. In opaque media, the effect of refraction is difficult to measure due to absorption and scattering. In biological tissues, either water molecules or macromolecules such as proteins and pigments can absorb light. Absorption occurs when an electromagnetic wave interacts with an elastically bound charged particle, which then vibrates at the frequency of the electromagnetic wave. Scattering, on the other hand, takes place at frequencies not corresponding to the natural frequencies of these particles. Scattering can be elastic or inelastic, depending on whether or not there is energy absorption during the scattering process. Both absorption and scattering processes will be present in most tissues, which are considered turbid media.



Where:
V_r = Vibrational relaxation
T^* = Oxygen in triplet state
R^* = Free radical
S_0 = Photosensitizer in ground state
S_1 = Photosensitizer in singlet state

Figure 1 - Photodynamic therapy process.

The types of light interaction with tissue depend on the wavelength and on the properties of the medium irradiated. There are five categories of interaction: photochemical, thermal, photoablation, plasma-induced ablation, and photodisruption. These interactions depend on the total power density applied to the tissue. For clinical PDT, only photochemical interactions and possibly thermal interactions are important. PDT has been shown to be synergistic with sub-lethal hyperthermia (19). In pre-clinical trials of PDT alone, the power density is maintained low enough to avoid thermal interactions.

Of the major proteins of blood that absorb light, the most important quantitatively is hemoglobin. Hemoglobin has significant absorption near 425, 544, and 577 nm, necessitating illumination of tissue at wavelengths >600 nm to ensure significant penetration. At wavelengths >1200 nm, light absorption by water molecules becomes substantial. For wavelengths >850-900 nm, the photons may not have sufficient energy to participate in a photochemical reaction. Therefore, the wavelength range between 600 and 800 nm has been determined as the practical "therapeutic window" for clinical PDT (Figure 2).

Photosensitization can also be affected within tissue by the presence of endogenous chromophores such as melanin, which competes with the photosensitizer for absorption of light. This is relevant when treating darker skinned patients or hyperpigmented lesions of metastatic melanoma. The absorption of light by the photosensitizer itself can limit light penetration in tissue, a phenomenon called photosensitizer self-shielding (15). In addition, the excited-state photosensitizer molecule can undergo a side reaction leading to loss of absorbance and photosensitizing ability (a process called photobleaching) (15). This process can modify the reciprocity between photosensitizer level and light, since with irradiation there will be a progressive loss of sensitizer. Photobleaching can be an advantage because, as the photosensitizer near the surface bleaches, light can penetrate deeper into the tissue. After the completion of treatment, photobleaching can be used to accelerate the clearance of drug from the body (20).

Light sources

The light source for PDT can be an ordinary light bulb, a diode array emitting a broad band incoherent spectrum, or a laser. Initially, PDT was performed with broad-spectrum light sources such as xenon arc lamps or slide projectors equipped with red filters to eliminate short wavelengths. However, the light intensities are low with these devices. Furthermore, PDT using these sources is limited to directly accessible sites such as the skin. Such sources are still used for *in vitro* and pre-clinical *in vivo* studies of tumors implanted in or under the skin. The advantages of lamps as light sources for PDT are their relatively low cost, simplicity and reliability (21). However, they cannot be used for optical fiber delivery because of the poor coupling efficiency into single fibers.

Lasers have become the standard light sources for PDT applications, due to their

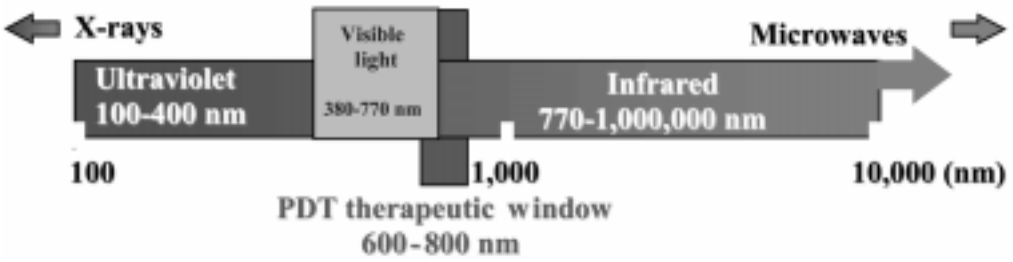


Figure 2 - Wavelength spectrum with the practical therapeutic window for PDT.

monochromatic character, high power output, and ease of coupling to fiber optics for endoscopic light delivery within a body cavity or for interstitial implants. Lasers can be used for both therapeutic and diagnostic applications in PDT. The most commonly used lasers for PDT are the tunable dye lasers, due to their versatility with respect to wavelength selection. The US FDA approved Photofrin® in conjunction with a specific device, either a laser system produced by LaserScope® (http://www.laserscope.com) or a system from Coherent® (http://www.cohr.com). The main disadvantage of pumped dye lasers is the high capital and running costs and poor reliability in the clinical environment. One of the more practical recent advances in PDT is the availability of diode lasers at wavelengths compatible with currently used photosensitizers (12). These systems have minimum electrical power requirement and are cooled thermoelectrically to provide a compact laser system. The potential advantages of the diode lasers for PDT are the low capital cost, negligible running costs, high reliability, small size and portability. These systems are very attractive for both clinical and pre-clinical investigations.

A laser delivery system for PDT consists of light source entrance optics, a beam guide, and target optics. Currently, coherent monochromatic lasers and single-strand optical fibers provide the flexibility needed to deliver light to subsurface lesions through surface, interstitial, intracavitary or endoscopic techniques. The choice of the delivery system will be governed by the characteristics of the laser system on the one hand and the tissue application on the other. The spatial distribution of a beam coming directly from the laser is usually of a gaussian shape (monomode) or a summation of gaussian profiles (multimode). The end of the fiber optic cable can be modified to shape the light to match the tissue to be treated. For example, introducing a lens at the end of the fiber optic spreads the beam uniformly over a specified area and can make the beam more uniform in intensity. These properties are important for the design and computation of target optics or modifications of the fiber tip. For a therapeutic system, the light on the target tissue can be seen and verified through the endoscope, either by eye or using a video camera. The tip of the fiberscope is usually maintained 1-2 cm from the target. An excellent overview of the evolution of endoscopic light delivery systems for PDT has recently been published (22).

Light dosimetry

The most important requirements for the diagnostic and therapeutic photoirradiation systems employed in PDT are that sufficient light must reach the target sites and its intensity must be properly verified at the treatment site by light detectors. There are four kinds of light detectors generally used in the optics field. The thermopile relies on the measurement of a temperature increase resulting from light absorbed in a material. Since the measurement is dependent upon significant thermal change, the use of a thermopile is limited to high power applications and is therefore well suited for laser operations. The photodiode directly converts light into an electrical current or voltage. Diodes show a large spectral sensitivity variation and must be calibrated at the wavelength of interest for quantitative measurements. Use of a diode is limited to low-to-medium power applications unless substantial attenuation of the light is present. The pyroelectric detector is based on the measurement of a current produced in a crystal by a change in its temperature. Its sensitivity is in the medium range and is limited to uses in medium power applications. The photomultiplier tube relies on photoelectric material to absorb a light photon and emit an electron. The sensitive photoelectric material and light gain from the dynode array multiplication of the photomultiplier tube make it extremely use-

ful in the detection of low light levels. These detectors have been used alone or in combination to verify light delivery before treating a tumor. The most common device for power measurement is the integrating sphere. The integrating sphere is a hollow sphere coated inside with barium sulfate, a diffuse white reflectance coating that offers greater than 97% reflectance between 450 and 900 nm. Integrating spheres are used as sources of uniform radiance and as input optics for measuring total power.

The success of PDT is dependent among other factors on the total light dose delivered into the target tissue (Table 1). The unit giving the total energy delivered is the joule (J) and is determined by watt (W) multiplied by time (s). The number of photons (N) in a joule depends upon the wavelength (λ) of the light. If two different wavelengths of light are used, the number of photons per joule varies as the inverse ratio of the wavelength (hc/λ, where $h = 6.623 \times 10^{-34}$ J is Planck's constant and $c = 2.998 \times 10^{8}$ ms^{-1} is the speed of light).

Another factor that must be considered in PDT is the delivered rate of the light (fluence rate = W/area). Fluence rate, and thus treatment time, depends on the light source used. If the light is delivered at a high rate, significant heating of a molecule and its surrounding may take place. Usually, fluence rates higher than 200 mW/cm^2 (for microlens) or 400 mW/cm (for cylindrical diffusers) are not used due to thermal effects that can damage the normal tissues.

Applying a given light intensity in W/area to the surface of a tissue does not imply that we know precisely what happens to the light intensity as the photons penetrate into the underlying tissue. It is necessary to measure light fluence within the tissue during the PDT session and the distribution of the photosensitizer to better quantify the effects of PDT. The ideal PDT irradiation would consist of optimizing the distribution of the delivered light to match the geometric distribution of the photosensitizer and the optical properties of the target tissue in order to minimize the damage to the surrounding normal tissues. Ascertaining the geometrical and optical properties of the target tissue and surrounding normal tissues for the individual patient is one of the more difficult aspects of PDT dosimetry. This requires both theoretical and experimental techniques for planning and monitoring the irradiation. Treatment planning is generally the physicist's responsibility, and it consists of optimizing the light delivery (balance between geometry, power density and treatment time) considering the laser system available.

It is not always possible to rely upon the reading of the laser display for accurate dosimetry during PDT. Although most lasers have a power calibration port on the system, the measurement cannot always be performed under conditions that are comparable with the clinical application. Since the concentration of the photosensitizer in tissue will affect the biological response, an acceptable means of measuring the photosensitizer in the target tissue and adjacent normal tissues is also desirable. The goal of light dosimetry is to optimize the distribution of the light dose in the treatment volume by selecting the best irradiation geometry. A recent publication (23) presented the concepts of light distribution in biological tissues in terms of simple expressions for spherical, cylindrical and planar geometry resulting from point sources, line sources (cylindrical diffusers), and planar sources (microlenses) which can be used as a guideline for clinical applications.

Central to light therapy planning is computation of the spatial distribution of the light dose in the target and surrounding tissues. The computational models are usually based on diffusion theory or Monte Carlo simulation. Predictions of the biological effect of the PDT require knowledge not only of the light within the target tissue but of the distribution of the photosensitizer as well.

Techniques to measure photosensitizer concentration non-invasively *in vivo* are being developed (24) using elastic scattering methods. The development of suitable computational models involves testing the dose predictions against experimental measurements using both *in vivo* and tissue-simulating phantoms (25).

Oxygen and oxygenation strategies for PDT

The efficacy of PDT with photosensitizers which localize in tumor tissue is most likely related to the yield of singlet oxygen ($^1O_2$) in the tumor (14). The yield of $^1O_2$, in turn, depends on the concentration of oxygen in the tissue (26). Some tumors may contain regions with oxygen concentrations too low for PDT to be optimally efficient (27). Both blood supply and oxygen consumption determine the amount of free oxygen available in a tissue. Truly hypoxic cells are thus very resistant to PDT. Tumor oxygenation may be improved by breathing a perfluorochemical emulsion or carbogen (95% O_2, 5% CO_2), which may modify the effect of PDT under certain conditions. The PDT reaction mechanism itself may consume oxygen at a rate sufficient to inhibit further PDT effects (28,29). It has been suggested that hyperbaric oxygen could enhance the PDT effect (30). In a recent study using the Walker 256 tumor model in Wistar rats, the enhancement of PDT effects under hyperbaric hyperoxia was demonstrated (31). The increased depth of tumor damage was evaluated by measuring histological sections following PDT treatment of tumors at 3 atmospheres (atm) and controls at 1 atm. *Ex vivo* morphometric analysis showed a total loss of cell viability in treated over control tissue. More experimental studies in this direction are warranted.

Another simpler approach for overcoming limitations of oxygen diffusion is to fractionate light delivery (e.g., 30 s on, 30 s off) or to reduce the fluence rate. Such protocols allow oxygen diffusion to compete with oxygen consumption and can provide improved tumor response (32,33).

Photosensitizers and clinical trials

Numerous clinical trials of PDT have been carried out (phase I, II, III and IV) for treatment of malignant lesions. PDT has been shown to be most efficacious for small tumors because of the light depth limitation. Photofrin® ($\lambda_{abs} \cong 630$ nm) is the first photosensitizer to be approved for clinical PDT, and additional trials are ongoing. Photofrin®-PDT is considered easier to perform than Nd-YAG ablation, and is especially advantageous in situations where Nd-YAG laser irradiation is difficult to carry out due to tumor location or tumor size such as found in advanced stage esophageal tumors (34). For lung cancer, Photofrin®-PDT has been approved for early and advanced non-small cell lung cancer. In these cases, it was concluded that PDT is superior to Nd-YAG irradiation for relief of dyspnea, cough, and hemoptysis. Photofrin®-PDT has been approved in Canada since 1993 for prophylactic treatment of papillary bladder tumors in patients at a high risk for recurrence. Photofrin®-PDT is being used in trials of high grade dysplasia as found in Barrett's esophagus. Biel (35) has reported excellent results in treatment of early stage head and neck cancer. Photofrin®-PDT has been tested also for adjuvant therapy such as combining PDT with resection of brain tumors (36,37), surgery for pleural cancers, especially malignant mesothelioma (38) and debulking surgery for intraperitoneal tumors (39).

In addition, several second-generation photosensitizers are undergoing clinical testing. These second-generation compounds are generally pure, can be activated by light in the range of 630-800 nm, and share in common a lower incidence of prolonged cutaneous photosensitivity than Photofrin®. One of

Table 1 - The basic units used in photodynamic therapy.

	Name (definition)	Concept (symbol)
Photosensitizer	Drug dose	mg/kg body weight or mg/m^2
	Drug concentration	mg drug/g tissue
	Wavelength of light absorption	λ_{abs} (nm = 10^{-9} m)
Light delivery	Number of photons	N
	Energy of photons	Joule (J)
	Energy density, fluence, intensity	J/cm^2 (microlens) or J/cm (cylinder diffuser)
	Power, radiant power, radiant energy flux	Watt (W) = J/s
	Power density, fluence rate, irradiance	W/cm^2 (microlens) or W/cm (cylinder diffuser)
	Optical penetration	δ (cm)
Oxygen	Partial pressure	atm = kgf/cm^2, mmHg, torr
	Concentration	mM (10^{-6} M)
Results	Treatment penetration depth	z (cm)

these is δ-aminolevulic acid (ALA or Levulan®; DUSA Pharmaceuticals, Toronto, Ontario, Canada; $\lambda_{abs} \cong 630$ nm), a precursor to the photosensitive protoporphyrin IX in the heme biosynthetic pathway. A limitation of Photofrin® and ALA is their low extinction at their absorption peak furthest into the red region (630 nm). Promising clinical results have been obtained using ALA in a variety of superficial malignant and nonmalignant lesions such as squamous cell carcinoma of the skin, Bowen's disease, mycosis fungoides, psoriasis (40,41) and solar keratosis (21).

Benzoporphyrin derivative monoacid ring A (BPD-MA or Verteporfin®; QLT Phototherapeutics Inc.; $\lambda_{abs} \cong 692$ nm) is a liposomal formulation. It appears to be useful for the treatment of age-related macular generation and choroidal melanoma (42). BPD-PDT also has been tested for treatment of atherosclerotic plaques (43) and psoriasis (44,45).

Lutetium texaphyrin/Lutex (Lutrin™; Pharmacyclics, Sunnyvale, CA, USA; $\lambda_{abs} \cong$ 732 nm) is a water-soluble photosensitizer that recently entered phase I clinical trials. It accumulates preferentially in malignant tissue (via an increased lipoprotein receptor mechanism). Lutex has been tested for photodynamic therapy of cardiovascular disease and for treatment of certain skin lesions (46).

Tin ethyl etiopurpurin (SnET2 or Purlytin®; Miravant, Santa Barbara, CA, USA; $\lambda_{abs} \cong 664$ nm) is being used in a phase II/III open-label, randomized study for women with advanced breast cancer and Kaposi's sarcoma in patients with AIDS, and phase I/II clinical testing for age-related macular degeneration. FDA has given its approval to begin a clinical study of Purlytin® for prostate cancer as well (47).

Tetra(m-hydroxyphenyl)chlorin (mTHPC or Foscan®; Scotia Pharmaceuticals, Kentville, Nova Scotia, Canada; $\lambda_{abs} \cong 652$ nm) is undergoing clinical testing in recurrent head and neck cancers in Europe and the US (48), and mono-L-aspartyl chlorin e6 (NPe6; $\lambda_{abs} \cong 664$ nm) has recently entered clinical trials for superficial malignancies of the skin and nasopharynx (49).

An advantage of using ALA, BPD-MA, and Lutex for PDT treatment is the ability to complete both drug administration and light exposure on the same day as a routine office procedure (41).

The silicon phthalocyanine (Pc 4; $\lambda_{abs} \cong$ 670 nm) is a new promising second-generation photosensitizer developed at Case Western Reserve University and University Hospitals of Cleveland (50). With the assistance

of the Drug Decision Network of the US National Cancer Institute, Pc 4 has completed evaluation of pre-clinical pharmacokinetics, efficacy and toxicology and has been recommended for clinical testing. Among the desirable features of Pc 4 are its chemical purity, its high extinction coefficient ($\varepsilon > 2 \times 10^5$ at 672 nm) affording deep tissue penetration of light, and its rapid clearance from skin, limiting the extent and duration of cutaneous photosensitivity. Considerable biological data regarding the efficacy of Pc 4-PDT are available in human tumor cells *in vitro* and in xerografts systems as well as in animal tumors (10,11,51,52). A potential advantage of Pc 4-PDT is its target-

Table 2 - PDT clinical applications.

Every effort was made to compile all the published protocols.

Application	Photosensitizer	Fluence (time after infusion)	Reference
Esophageal			
Advanced stage cancer	2.0 mg/kg Photofrin®	50-200 J/cm (48 h)	2
	1.4 mg/kg DHE	300 J/cm (2-3 days)	54
Barrett's esophagus cancer	2.0 mg/kg Photofrin®	200 J/cm (40-50 h)	54
	1.4 mg/kg DHE	400 J/cm (24-72 h)	2
Pulmonary			
Advanced non-small cell lung cancer			
Early stage lung cancer (<2 cm)	2.5 mg/kg Photofrin®	200-400 J/cm (2-4 days)	55
	2.0 mg/kg Photofrin®	100-200 J/cm	56
	1.0-2.0 mg/kg Photofrin®	200-300 J/cm (48 h)	56
	2.0 mg/kg Photofrin®	200-300 J/cm (48 h)	57
Endobronchial tumors			
Trachea and main bronchi	1.4 mg/kg DHE	400 J/cm (2-7 days)	2
	2.0 mg/kg Photofrin®	100-200 J/cm	2
Lobe bronchi	1.4 mg/kg DHE	300 J/cm (2-7 days)	2
Segmental bronchi or carcinoma *in situ*	1.4 mg/kg DHE	200 J/cm (2-7 days)	
Skin			
Melanoma	10-20 µmol/kg Lutex	150-600 J/cm^2 (3, 5, 24 h)	46
Cutaneous metastatic breast cancer	1.2 mg/kg SnET2	200 J/cm^2	47
Recurrent adenocarcinoma of the breast	2.5-3.5 mg/kg NPe6	100 J/cm^2 (4 h)	20
Small basal cell carcinoma and breast cancer	1.0 mg/kg Photofrin®	100 J/cm^2	20
Kaposi's sarcoma (AIDS patients)	1.2 mg/kg SnET2	200 J/cm^2	20
Skin cancer	0.5-3.5 mg/kg NPe6	150 J/cm^2 (3 h)	20
Bowen's disease	1.0 mg/kg Photofrin®	25-100 J/cm^2	58
Skin disorders with topically applied PDT	20% Levulan®	185-250 J/cm^2	40,41
		10 J/cm^2 (3 h)	
Head and Neck			
Early stage cancer	2.0 mg/kg Photofrin®	50-75 J/cm^2 (48 h)	35
		100 J/cm (48 h, tumor >3 cm)	35
Head and neck cancer	0.1 mg/kg Foscan®	10 J/cm^2	59
Early stage squamous cell carcinoma	0.3 mg/kg Foscan®	8-12 J/cm^2 (4 days)	48
Oral cavity	2.0 mg/kg Photofrin®	50-75 J/cm^2	48
Larynx	2.0 mg/kg Photofrin®	80 J/cm^2	48
Bladder			
Superficial cancer	1.5 mg/kg Photofrin®	15 J/cm^2	60
Intrathoracic tumor			
Thoracic cavity	2.0 mg/kg Photofrin®	15-35 J/cm^2 (48 h)	38
Intraperitoneal tumors			
Pleural cancer	1.5-2.5 mg/kg Photofrin®	2.8-3.0 J/cm^2 (48-72 h, *iv*)	39
Brain tumors			
Glioblastoma or astrocytoma	2.0 mg/kg Photofrin®	1800 J	37

ing of the tumor parenchyma (52).

Table 2 shows the current status of PDT treatment and the time after drug injection generally used for the clinically approved and experimental photosensitizers.

Conclusion

Photodynamic therapy is a potentially effective and safe treatment approach for superficial human cancers and selected benign conditions. The technique can be used as an adjuvant therapy with surgery, radiation or chemotherapy. Major late effects are limited to skin photosensitization for up to 6 weeks after Photofrin® injection. Newer generation photosensitizers are being tested which may produce less photosensitivity.

PDT is an exciting multi-disciplinary area involving research and direct clinical application of the research. A cancer center is multi-disciplinary in nature making it a natural environment for a PDT center. It provides alternative therapy for many patients who cannot have any other type of treatment, and it also benefits medical education. Refinement of this technique will require collaborative research efforts in several fields, including chemical synthesis, pharmacokinetics of the photosensitizers to establish optimum treatment times, physics to develop better light sources and delivery methods to ensure proper light delivery, and to improve treatment through visualization of the target.

One of the most pressing issues in dealing with the several clinical trials being implemented is the issue of light dosimetry and the proper delivery of light dose. Usually, the light dose is given in terms of external power density delivered by the light system. The light dose actually received by the photosensitizer and tissue may be higher or lower depending on the geometry of irradiation. A proper definition of light dose is also needed. An attempt to define light dose similar to what is used in radiation oncology was attempted by Profio and Doiron (53). The use of this definition calls for knowledge of the photosensitizer concentration in tissue, which is not yet known. Another issue is quality assurance of the treatment. Presently, most treatments are done without proper verification of the equipment, whether or not the light distribution is uniform, the light delivery system is properly calibrated, and if the patient has been properly immobilized. To ensure optimum treatment and comparison between results of different clinical trials, a quality assurance program of treatment method and light delivery should be established. Finally, the future progress of photodynamic therapy will require input from physics, engineering, and computer science to develop models for light dosimetry and treatment planning.

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