Photodynamic Therapy of Cancer: An Update

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Abstract

Photodynamic therapy (PDT) is a clinically approved, minimally invasive therapeutic procedure that can exert a selective cytotoxic activity toward malignant cells. The procedure involves administration of a photosensitizing agent followed by irradiation at a wavelength corresponding to an absorbance band of the sensitizer. In the presence of oxygen, a series of events lead to direct tumor cell death, damage to the microvasculature, and induction of a local inflammatory reaction. Clinical studies revealed that PDT can be curative, particularly in early stage tumors. It can prolong survival in patients with inoperable cancers and significantly improve quality of life. Minimal normal tissue toxicity, negligible systemic effects, greatly reduced long-term morbidity, lack of intrinsic or acquired resistance mechanisms, and excellent cosmetic as well as organ function-sparing effects of this treatment make it a valuable therapeutic option for combination treatments. With a number of recent technological improvements, PDT has the potential to become integrated into the mainstream of cancer treatment. **CA Cancer J Clin 2011;61:250-281. ©2011 American Cancer Society, Inc.**

Introduction

Despite progress in basic research that has given us a better understanding of tumor biology and led to the design of new generations of targeted drugs, recent large clinical trials for cancer, with some notable exceptions, have been able to detect only small differences in treatment outcomes.[1,2] Moreover, the number of

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Some of the figures were produced with the help of Abhishek Garg using Servier Medical Art (available at www.servier.com) for which we would like to acknowledge Servier.

DISCLOSURES: Supported by the Fund for Scientific Research (FWO)-Flanders (Belgium) (grant numbers G.0661.09 and G.0728.10), the Interuniversity Attraction Pole IAP6/18 of the Belgian Federal Government, and the Catholic University of Leuven (OT/06/49 and GOA/11/009) (to P.A.); National Institutes of Health (NIH) grant CA-087971 (to K.A.C. and S.M.H.); NIH grants CA72630, CA70823, and HL85677 (to A.W.G.); NIH grants CA55791 and CA98156 (to S.O.G.); NIH grants CA68409 and CA122093 (to T.H.F.); NIH grants AI050875 and CA083882 (to M.R.H.); and the European Regional Development Fund through Innovative Economy grant POIG.01.01.02-00-008/08 (to J.G.). Dr. Kessel's research has been supported by NIH grants since 1980, predominantly by CA23378. Dr. Juzeniene' research has been supported by the Norwegian Cancer Society. Dr. Mroz was partly supported by a Genzyme-Partners Translational Research Grant. Dr. Golab is a recipient of the Mistrz Award from the Foundation for Polish Science and a member of the TEAM Programme cofinanced by the Foundation for Polish Science and the European Union European Regional Development Fund.

 doi:10.3322/caac.20114.

TABLE 1. Glossary of Specialty Terms

SPECIALTY TERM	DEFINITION
Chaperone	A protein that participates in the folding of newly synthesized or unfolded proteins into a particular 3-dimensional conformation.
Damage-associated molecular patterns (DAMPs)	Intracellular proteins that, when released outside the cell after its injury, can initiate or sustain an immune response in the noninfectious inflammatory response.
Fluence rate	The number of particles that intersect a unit area in a given amount of time (typically measured in watts per m^2).
Fluorescence-guided resection	A technique to enhance contrast of viable tumor borders that uses fluorescence emission from tissue. Fluorescence can be enhanced by the addition of exogenous chromophores (such as photosensitizers) with specific absorption and fluorescence properties.
Ground state	A state of elementary particles with the least possible energy in a physical system. This is the usual (singlet) state of most molecules. One of the exceptions includes oxygen, which in its ground state is a triplet and can be converted to a higher energy state of singlet oxygen during photodynamic therapy.
Immunocompromised mice	Animals having an immune system that has been impaired by genetic modification, disease, or treatment.
Immunocompetent mice	Animals having an intact (ie, normally functioning) immune system.
Intersystem crossing	A radiationless process in which a singlet excited electronic state makes a transition to a triplet excited state.
Macromolecular therapeutics	Proteins such as antibodies and growth factors for cell surface targeting, peptides and mRNA for cancer vaccination, and nucleotides for gene delivery and silencing as well as drug moieties such as polymers and nanoparticles for the delivery of therapeutics.
Major histocompatibility complex class I molecules	Transmembrane glycoproteins that bind short 8-11 amino acid long peptides recognized by T-cell receptors.
Naïve mice	Nonimmunized animals (ie, those that were not previously exposed to a particular antigen [such as tumor-associated antigen]).
Pathogen-associated molecular patterns (PAMPs)	Evolutionary conserved microbial molecules that are not normally produced by mammalian cells and are often common to whole classes of micro-organisms. PAMPs are recognized by pattern-recognition receptors.
Pattern-recognition receptors	Receptors for detection of DAMPs and PAMPs, initiating signaling cascades that trigger innate immune response.
Photosensitizer	A light-absorbing compound that initiates a photochemical or photophysical reaction.
Singlet oxygen ($^1O_2$)	An excited or energized form of molecular oxygen characterized by the opposite spin of a pair of electrons that is less stable and more reactive than the normal triplet oxygen (O_2).
Triplet state	A state of a molecule or a free radical in which there are 2 unpaired electrons.
Ubiquitin-proteasome system	The major intracellular pathway for protein degradation.

new clinically approved drugs is disappointingly low.[3] These sobering facts indicate that to make further progress, it is necessary to put an emphasis on other existing but still underappreciated therapeutic approaches. Photodynamic therapy (PDT) has the potential to meet many currently unmet medical needs. Although still emerging, it is already a successful and clinically approved therapeutic modality used for the management of neoplastic and nonmalignant diseases. PDT was the first drug-device combination approved by the US Food and Drug Administration (FDA) almost 2 decades ago, but even so remains underutilized

PDT consists of 3 essential components: photosensitizer (PS) (see Table 1 for the definitions of specialty terms), light, and oxygen.[4,5] None of these is individually toxic, but together they initiate a photochemical reaction that culminates in the generation of a highly reactive product termed singlet oxygen ($^1O_2$) (Table 1). The latter can rapidly cause significant toxicity leading to cell death via apoptosis or necrosis. Antitumor effects of PDT derive from 3 inter-related mechanisms: direct cytotoxic effects on tumor cells, damage to the tumor vasculature, and induction of a robust inflammatory reaction that can lead to the development of systemic immunity. The

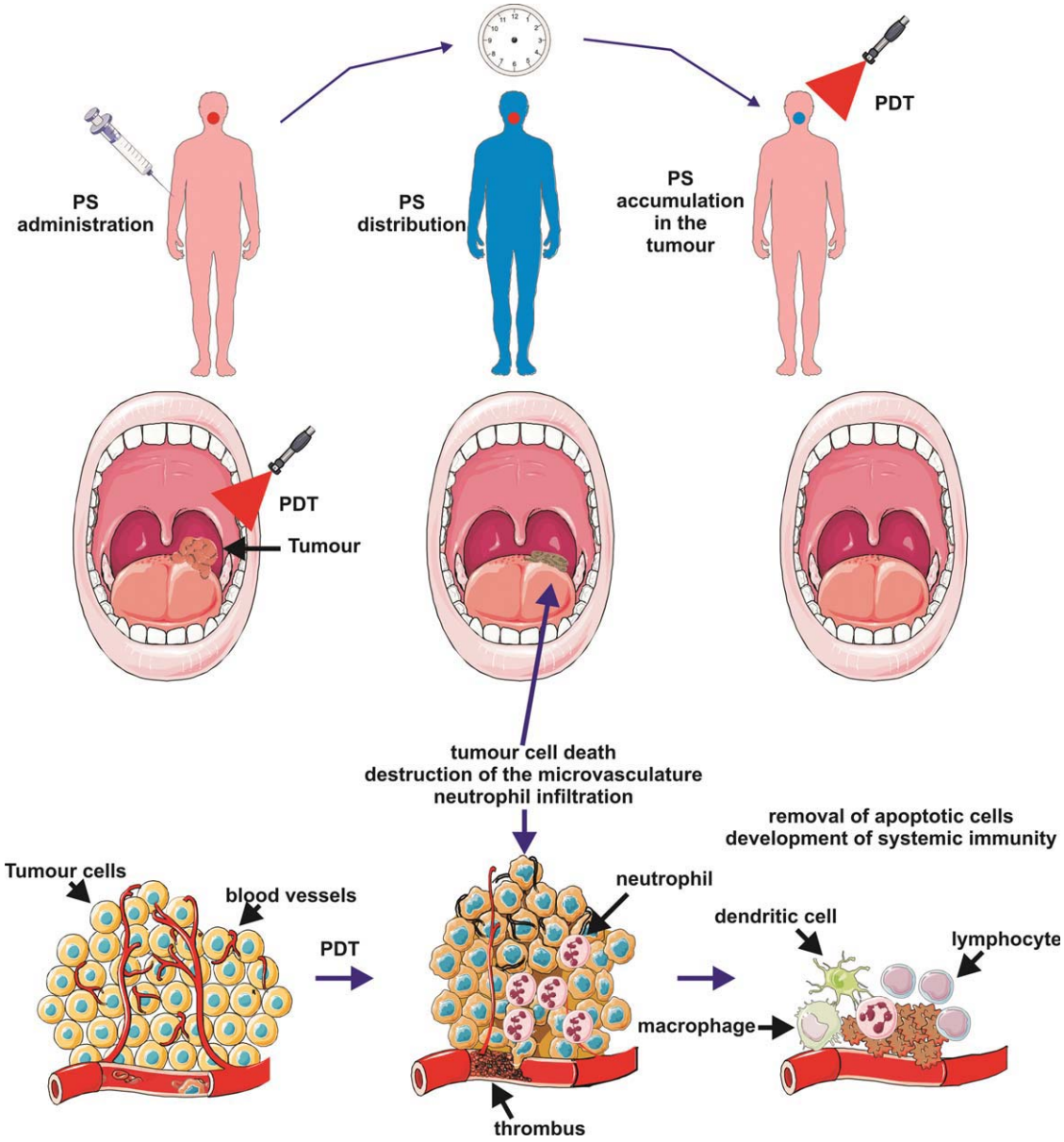

FIGURE 1. The Principles of Photodynamic Therapy (PDT). A photosensitizer (PS) is administered systemically or topically. After a period of systemic PS distribution it selectively accumulates in the tumor. Irradiation activates the PS and in the presence of molecular oxygen triggers a photochemical reaction that culminates in the production of singlet oxygen ($^1O_2$). Irreparable damage to cellular macromolecules leads to tumor cell death via an apoptotic, necrotic, or autophagic mechanism, accompanied by induction of an acute local inflammatory reaction that participates in the removal of dead cells, restoration of normal tissue homeostasis, and, sometimes, in the development of systemic immunity.

a large extent on the type and dose of PS used, the time between PS administration and light exposure, total light dose and its fluence rate (Table 1), tumor oxygen concentration, and perhaps other still poorly recognized variables. Therefore, determination of optimal conditions for using PDT requires a coordinated interdisciplinary effort. This review will address the most important biological and physicochemical aspects of PDT, summarize its clinical status, and provide an outlook for its potential future

Basic Components of PDT

PDT is a 2-stage procedure. After the administration of a light-sensitive PS, tumor loci are irradiated with a light of appropriate wavelength. The latter can be delivered to virtually any organ in the body by means of flexible fiber-optic devices (Fig. 1). Selectivity is derived from both the ability of useful PSs to localize in neoplastic lesions and the precise delivery of light to the treated sites. Paradoxically, the highly

limitations, because the treatment is ineffective against metastatic lesions, which are the most frequent cause of death in cancer patients. Ongoing research is focused on finding optimal PDT conditions to induce systemic immunity that might, at least to some extent, obviate this limitation in the future. PDT can be used either before or after chemotherapy, radiotherapy, or surgery without compromising these therapeutic modalities. None of the clinically approved PSs accumulate in cell nuclei, limiting DNA damage that could be carcinogenic or lead to the development of resistant clones. Moreover, the adverse effects of chemotherapy or radiation are absent. Radioresistance or chemoresistance do not affect sensitivity to PDT. Excellent cosmetic outcomes make PDT suitable for patients with skin cancers. There are no significant changes in tissue temperature, and the preservation of connective tissue leads to minimal fibrosis, allowing retention of functional anatomy and mechanical integrity of hollow organs undergoing PDT. Selected patients with inoperable tumors, who have exhausted other treatment options, can also achieve improvement in quality of life with PDT. Finally, many PDT procedures can be performed in an outpatient or ambulatory setting, thereby not only alleviating costs, but also making the treatment patient-friendly. The only adverse effects of PDT relate to pain during some treatment protocols and a persistent skin photosensitization that has been circumvented by the newer agents.

Photosensitizers

Most of the PSs used in cancer therapy are based on a tetrapyrrole structure, similar to that of the protoporphyrin contained in hemoglobin. An ideal PS agent should be a single pure compound to allow quality control analysis with low manufacturing costs and good stability in storage. It should have a high absorption peak between 600 and 800 nanometers (nm) (red to deep red), because absorption of photons with wavelengths longer than 800 nm does not provide enough energy to excite oxygen to its singlet state and to form a substantial yield of reactive oxygen species. Because the penetration of light into tissue increases with its wavelength, agents with strong absorbance in the deep red such as chlorins, bacteriochlorins, and phthalocyanines offer improve-

toxicity and relatively rapid clearance from normal tissues, thereby minimizing phototoxic side effects. Other pertinent desirable properties of PS agents have been summarized elsewhere.[6] Although the interval between drug administration and irradiation is usually long, so that the sensitizer is given sufficient time to diffuse from normal tissues, reports now suggest that the tumor response may be sometimes better when light is delivered at a shorter drug-light interval when PS is still present in the blood vessels, thus producing marked vascular damage.[7] Some reports suggest that a pronounced inflammatory response and necrotic cell death after illumination are important in the immune-stimulating function of PDT, whereas others suggest that PSs that produce more apoptosis and less inflammation are suitable for applications such as brain tumors, where swelling is undesirable. Recent findings show that certain PDT-induced apoptotic cell death mechanisms are highly immunogenic and capable of driving antitumor immunity as well.[8] Finally, the light-mediated destruction of the PS known as photobleaching was previously thought to be undesirable, but some reports suggest that this property may make light dosimetry less critical because overtreatment is avoided when the PS is destroyed during the illumination.[9]

The first PS to be clinically employed for cancer therapy was a water-soluble mixture of porphyrins called hematoporphyrin derivative (HPD), a purified form of which, porfimer sodium, later became known as Photofrin. Although porfimer sodium is still the most widely employed PS, the product has some disadvantages, including a long-lasting skin photosensitivity and a relatively low absorbance at 630 nm. Although a photodynamic effect can be produced with porfimer sodium, efficacy would be improved by red-shifting the red absorbance band and increasing the absorbance at the longer wavelengths. There has been a major effort among medicinal chemists to discover second-generation PSs, and several hundred compounds have been proposed as potentially useful for anticancer PDT. Table 2 displays the most promising PSs that have been used clinically for cancer PDT (whether approved or in trials). The discovery that 5-aminolevulinic acid (ALA) was a biosynthetic precursor of the PS protoporphyrin IX[10] has led to many applications in which ALA or ALA esters can be topically applied or administered orally. These are considered to be

TABLE 2. Clinically Applied Photosensitizers

PHOTOSENSITIZER	STRUCTURE	WAVELENGTH, nm	APPROVED	TRIALS	CANCER TYPES
Porfimer sodium (Photofrin) (HPD)	Porphyrin	630	Worldwide		Lung, esophagus, bile duct, bladder, brain, ovarian
ALA	Porphyrin precursor	635	Worldwide		Skin, bladder, brain, esophagus
ALA esters	Porphyrin precursor	635	Europe		Skin, bladder
Temoporfin (Foscan) (mTHPC)	Chlorine	652	Europe	United States	Head and neck, lung, brain, skin, bile duct
Verteporfin	Chlorine	690	Worldwide (AMD)	United Kingdom	Ophthalmic, pancreatic, skin
HPPH	Chlorin	665		United States	Head and neck, esophagus, lung
SnEt2 (Purlytin)	Chlorin	660		United States	Skin, breast
Talaporfin (LS11, MACE, NPe6)	Chlorin	660		United States	Liver, colon, brain
Ce6-PVP (Fotolon), Ce6 derivatives (Radachlorin, Photodithazine)	Chlorin	660		Belarus, Russia	Nasopharyngeal, sarcoma, brain
Silicon phthalocyanine (Pc4)	Phthalocyanine	675		United States	Cutaneous T-cell lymphoma
Padoporfin (TOOKAD)	Bacteriochlorin	762		United States	Prostate
Motexafin lutetium (Lutex)	Texaphyrin	732		United States	Breast

Abbreviations: ALA, 5-aminolevulinic acid; AMD, age-related macular degeneration; Ce6-PVP, chlorin e6-polyvinypyrrolidone; HPD, hematoporphyrin derivative; HPPH, 2- (1-hexyloxyethyl)-2-devinyl pyropheophorbide-a; MACE, mono-(L)-aspartylchlorin-e6; mTHPC, m-tetrahydroxyphenylchlorin; nm indicates nanometers; SnEt2, tin ethyl etiopurpurin.

to be active PSs. Many hypotheses have been proposed to account for the tumor-localizing properties in PDT.[11] These include the preponderance of leaky and tortuous tumor blood vessels due to neovascularization and the absence of lymphatic drainage known as the enhanced permeability and retention effect.[12] Some of the most effective compounds bind preferentially to low-density lipoprotein (LDL), suggesting that upregulated LDL receptors found on tumor cells could be important.[13]

There have been targeting studies in which PSs are covalently attached to various molecules that have some affinity for neoplasia or to receptors expressed on specific tumors.[14] The intention is to rely on the ability of the targeting vehicle to control localization factors so that the PS can be chosen based on its photochemical properties. These vehicles include monoclonal antibodies, antibody fragments, peptides, proteins (such as transferrin, epidermal growth factor and insulin), LDL, various carbohydrates, somatostatin, folic acid, and many others.

Light Sources

Blue light penetrates least efficiently through tissue, whereas red and infrared radiations penetrate more is often called the optical window of tissue. However, light up to only approximately 800 nm can generate $^1O_2$, because longer wavelengths have insufficient energy to initiate a photodynamic reaction.[15] No single light source is ideal for all PDT indications, even with the same PS. The choice of light source should therefore be based on PS absorption (fluorescence excitation and action spectra), disease (location, size of lesions, accessibility, and tissue characteristics), cost, and size. The clinical efficacy of PDT is dependent on complex dosimetry: total light dose, light exposure time, and light delivery mode (single vs fractionated or even metronomic). The fluence rate also affects PDT response.[16] Integrated systems that measure the light distribution and fluence rate either interstitially or on the surface of the tissues being treated are so far used only in experimental studies.

Both lasers and incandescent light sources have been used for PDT and show similar efficacies.[17] Unlike the large and inefficient pumped dye lasers, diode lasers are small and cost-effective, are simple to install, and have automated dosimetry and calibration features and a longer operational life. Such lasers are now being specifically designed for PDT.

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