

REVIEW ARTICLE

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Photodynamic therapy: A new modality treatment in pre-cancer and cancer patients

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ABSTRACT

Introduction: Photodynamic therapy (PDT) is a new modality of therapy being used for the diagnosis and treatment in pre-cancer and cancer patients and various skin diseases. Photodynamic therapy is a powerful light-initiated photochemical reaction, involving the use of a photoactive dye (photosensitizer) activated by light of a specific wavelength in the presence of oxygen. This leads to the formation of oxygen free radicals which are toxic, which can damage proteins, lipids, nucleic acids and other components. Application of photodynamic therapy in dentistry is growing rapidly for the use of oral pre-cancers and cancer lesions, bacterial and fungal infections. Photodynamic antimicrobial chemotherapy (PACT) has been efficacious in the management of periodontal infections, peri-implantitis, endodontic infections and oral bio-films formation. The absence of genotoxic and mutagenic effects and no risk of developing resistance to its antimicrobial action made its use important.

Photodynamic therapy is limited to superficial lesions at present. However, in future a deeper effect can be achieved by the developments in this technique. This review gives a general summary of the mechanism and clinical applications of photodynamic therapy.

Keywords: Photodynamic therapy (PDT), Photosensitizers, Photodynamic Antimicrobial chemotherapy (PACT)

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INTRODUCTION

Photodynamic therapy (PDT) is a medical treatment and it is a promising new approach for the treatment of cancers. It utilizes light to activate a photoactive dye (photosensitizer) in the presence of oxygen. This results in the formation of oxygen species, such as singlet oxygen and free radicals, causing localized photo damage and cell death. Clinically, this reaction is cytotoxic and vasculotoxic. Photodynamic therapy is also known as photoradiation therapy, phototherapy, or photochemical therapy. It also has antimicrobial properties. Photodynamic antimicrobial chemotherapy (PACT) includes an alternative antibacterial, antifungal and antiviral treatment for drug resistant organisms. Now-a-day's applications of PDT in dentistry are growing rapidly in the treatment of oral cancer, bacterial and fungal infections and the photodynamic diagnosis (PDD)

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of the malignant transformation of oral lesions. The non-oncological applications of PDT include treatment of psoriasis, actinic keratosis, rheumatoid arthritis, and age-related macular degenerations [1].

HISTORY

The use of sunlight for the treatment of various skin disorders (heliotherapy) in ancient Indians and Greeks was present. The early 1900s lead to the discovery of photodynamic therapy by a German medical student, Oscar Raab observed by chance that the dye, acridine orange in the presence of light was toxic to protozoa (*Paramecium caudatum*) [2, 3]. His professor, Von Tappeneir, coined the term ‘photodynamic’ to describe oxygen consuming chemical reactions in vivo. In 1904, von Tappeiner and Jesionek (a dermatologist) used topical eosin and visible light to treat skin tumors, condyloma lata and lupus vulgaris [4, 5]. The first study on humans performed by German physician Friedrich Meyer–Betz with Porphyrins on his own skin in 1913 and named it photoradiation therapy (PRT) [6]. Photodynamic effects on tumors were reported until 1942 by Auler and Banzer, who injected tumor-bearing animals with hematoporphyrin and exposed them to a quartz–halogen lamp, observing necrosis and fluorescence of tumors [2, 7]. Dougherty et al. demonstrated a partial or complete response in tumors in humans when hematoporphyrin derivative (HpD) and light at 630 nm were used together [2, 8]. Hayata et al. the first to use fibroptic laser exposure to treat early bronchial cancer with PDT in 1982 [2, 9].

It was John Toth, who acknowledged the “photodynamic chemical effect” of the therapy with early clinical argon dye lasers and renamed ‘photodynamic therapy’. Photodynamic therapy received even greater interest as Thomas Dougherty formed the international photodynamic association, in 1986. Its use first started in dermatology (1992), then oncology (1995), and recently in microbiology (1996) [10].

Photodynamic therapy involves three components light source (Figure 1), photosensitizing agent (photosensitizer) and tissue oxygen [1].

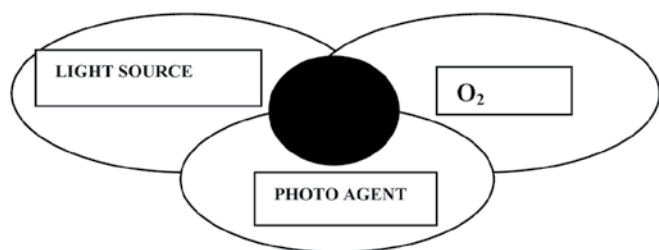


Figure 1: Photodynamic therapy involves three components—light source, photosensitizer and tissue oxygen.

LIGHT SOURCE

Photodynamic therapy requires a source of light that activates the photosensitizers (photo-active dye) by exposure to low-power visible light at a specific wave length. The therapeutic window for PDT is between 630 nm and 1200 nm as a light of wavelength, below 630 nm is absorbed by hemoglobin in the tissues and above 1200 nm is absorbed by water [11]. Human tissue transmits red light between 630 nm and 700 nm efficiently, and longer wavelength of the photosensitizers results in deeper light penetration. Most photosensitizers are activated by red light between 630 nm and 700 nm, penetration depth from 0.5 cm (at 630 nm) to 1.5 cm (at 700 nm) [1]. In the past, various variety of light sources, such as argon-pumped dye lasers, potassium titanyl phosphate (KTP) or neodymium: yttrium aluminium garnet (Nd/YAG)-pumped dye lasers, and gold vapor-pumped or copper vapor-pumped dye lasers were used. All these are complex systems and expensive. At present diode laser are used which are easy to handle, portable, and cost effective [1]. Non-coherent light sources, such as tungsten filament, quartz halogen, xenon arc, metal halide, and phosphor-coated sodium lamps are used for treatment of larger areas. Recently, non-laser light sources, are used mostly, such as light-emitting diodes (LED) which are much less expensive, small, lightweight, and highly flexible [1]. The absorption of light source by tissues is wavelength-dependent and tissue-penetration is greater at longer wavelengths [2]. The total light dose, the dose rates, and the depth of destruction vary with each tissue treated and with each photosensitizer [1].

The following are light sources specifically designed for PDT [11]:

1. Red light emission for large surface areas-metal halogen lamp (600–800 nm high power density).
2. Short arc xenon lamp (400–1200 nm).

PHOTOSENSITIZING AGENTS

A Photosensitizer is a chemical compound (usually a dye) is administered (injected or applied topically) to the patient and gets accumulated into the tissues. The tissue is then irradiated with light of a specific wavelength. Thousands of natural and synthetic photoactive compounds have photosensitizing potential. They include degradation products of chlorophyll, polyacetylenes, thiopenes, quinines, antraquinones, and 9-methoxypsoralen [1]. The majority of the photosensitizers used clinically belong to dyes, the porphyrins, chlorins, and furocoumarins.

Ideal photosensitizers should be: [1]

- Non-toxic
- Local toxicity only after activation by light source
- Accumulate maximally in tumors in short time
- High quantum yield of singlet oxygen production in vivo

- Cost effectiveness and commercial availability
- High solubility in water, injection solutions, and blood substitutes
- Short half-life period
- Rapid clearance from tissues.
- Storage and application light stability.

The various photosensitizing agents can be grouped under three generations.

First generation

The following are second generation photosensitizer:

- Photofrin dihematoporphyrin-ester (DHE)
- Hematoporphyrin derivatives (HPDs).

DHE under the commercial name of Photofrin has been most commonly used, the depth of necrosis achieved by Photofrin induced PDT is about 0.5 cm. It has no systemic toxicity except prolonged photosensitivity (approximately 6–8 weeks) [2].

Second generation

The following are second generation photosensitizer:

- 5-Aminolevulinic acid (ALA)
- Benzoporphyrin derivative (BPD)
- Temoporfin Meta-Tetra-Hydroxy Phenyl Chlorin (mTHPC)
- Talaporfin sodium (LS11)
- Foscan (mTHPC)

5-Aminolevulinic acid (ALA) is an intrinsic photosensitizer that is converted in situ to a photosensitizer, Protoporphyrin-IX. The depth of necrosis produced by ALA induced PDT not more than 1.5 mm, therefore topical ALA and its esters have been used to treat pre-cancer conditions, and basal and squamous cell carcinoma of the skin [1, 2].

The advantage of ALA over HPDs is that, it is cleared from the body more rapidly. Foscan (m-THPC), the most potent drug, induced PDT offers deeper tumor destruction (1 cm) and larger tumors (up to stage T1 tumors) can be effectively treated [2].

Third generation

The following are third generation photosensitizer:

Currently available drugs are modified by targeting with monoclonal antibodies or with non-antibody based protein carriers and protein receptors, and conjugation with a radioactive tag [1].

Currently, only four photosensitizers are commercially available namely, Photofrin, ALA, Visudyne (verteporfin) and Foscan. The first three have been approved by FDA, while all four are in use in European countries [1].

MECHANISM OF ACTION

The efficacy of PDT depends on the following mechanisms (Figure 2), direct cytotoxicity, vascular damage, inflammation and immune host defence [11].

After irradiation with a light of specific wavelength the photosensitizer under goes a transition from its ground singlet state to an excited singlet state (has high energy

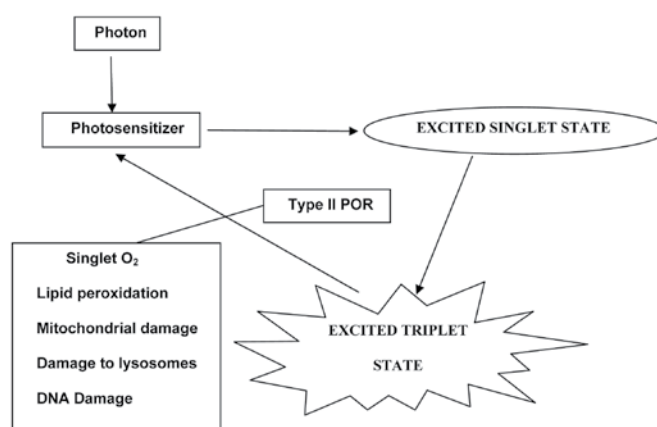


Figure 2: Mechanism of photodynamic therapy with in the cell.

and short-life span). The excited singlet state molecule may follow two pathways:

- The molecule may decay back to its ground state emitting fluorescence light. This fluorescence property has been used diagnostically for detecting the sensitizers in tissues and for tumor localization.
- For the photodynamic reaction, the molecule must convert to a excited triplet state (has lower energy and longer life span) [2].

The triplet state can react with endogenous oxygen present in the tissue to produce singlet oxygen (highly reactive) and other free radical species, causing a rapid and selective destruction of the target tissue. There are two mechanisms of this process:

- Type-I reaction involves electron transfer directly from the photosensitizer producing ions or electrons/hydrogen removal from a substrate molecule to form free radicals. These radicals react rapidly with oxygen, resulting in the production of highly reactive oxygen species (superoxide, hydroxyl radicals, and hydrogen peroxide).
- Type II photo-oxidation reaction (POR) produce the electronically excited and highly reactive state of oxygen (singlet oxygen).

These two reactions contribute equally in the photodynamic process of reaction [1, 11]

SIDE EFFECTS OF PHOTODYNAMIC THERAPY

The side effects of PDT are:

- The major side effect after the use of intravenous photosensitizers is photosensitivity.
- The systemic administration of the sensitizer results in residual skin photosensitivity, nausea, vomiting, metallic taste, and liver toxicity [11].
- Topically applied photosensitizer (ALA) reports burning sensation during illumination.

- Other side effects are coughing, trouble swallowing, stomach pain, painful breathing or shortness of breath. These side effects are usually temporary [1, 11].
- 5-Aminolevulinic acid may cause tachycardia and hypotension in patients with cardiovascular problems [2].

INDICATIONS OF PHOTODYNAMIC THERAPY

In 1993, Canada first approved PDT for prophylaxis of papillary bladder cancer.

Potential indications for PDT in oral medicine [11], dermatology and oncology are:

- Actinic keratosis
- Bowen disease
- Superficial squamous cell carcinoma and basal cell carcinoma
- Keratoacanthoma
- Kaposi's sarcoma
- Actinic cheilitis
- Cutaneous metastases
- Psoriasis vulgaris
- Malignant melanoma
- Early head and neck cancers
- Pre-malignant lesions and conditions in the oral cavity

ADVANTAGES OF PHOTODYNAMIC THERAPY

The advantages of PDT are [1, 10]:

- Photodynamic therapy is a localized therapy and it has only localized effects as the photosensitizer is selectively absorbed by the target tissues.
- Photodynamic therapy can be performed in out-patient or inpatient settings.
- Photodynamic therapy is more economical than radiation therapy and surgical therapy for cancer patients.
- Less invasive, no long-term side effects and can be repeated many times at the same site, if needed.
- Photodynamic therapy has excellent cosmetic results and the healing process results in little or no scarring.

LIMITATIONS OF PHOTODYNAMIC THERAPY

The limitations of PDT are [1, 10]:

- Light is needed to activate photosensitizers.
- Photosensitizers cannot penetrate more than 1.5 cm of tissue depth using with standard lasers and

low powered LED technology, and hence it is less effective in treatment of large tumors.

- Photodynamic therapy cannot be used in patients, who are allergic to porphyrins.

The PDT in pre-cancer and cancer lesions is as follows.

Leukoplakia

The following are first generation photosensitizer:

Oral leukoplakia, oral erythroplakia and oral verrucous hyperplasia (OVH) are three common oral precancerous lesions. The high malignant transformation rate of oral premalignant lesions highlights the importance of early detection and treatment.

Traditional treatment for oral pre-cancers is total surgical excision that always leads to scar formation. Photodynamic therapy is an effective treatment option for human precancerous lesions because it can be used repeatedly without cumulative side effects and results in little or no scar formation [12].

The application of photodynamic therapy in oral leukoplakia significantly reduces the time of treatment in comparison with pharmacological methods involving vitamin A or active metabolites of vitamin A. Application of vitamin A requires 2 to 3 months to complete cure [13].

In 1996, Fan et al. treated oral leukoplakia cases of 12 patients using orally administrated ALA-based PDT. All 12 patients showed regression of the lesions to normal or less dysplastic [1] In 1998, Kuber et al. treated 12 patients who had been suffering from leukoplakia of the oral mucosa for several years. ALA (20% cream) was applied to the leukoplakia lesion for 2 hours. Five patients showed complete response, four patients showed a partial response and in three patients showed no response. In 2005, Chen et al. treated oral verrucous hyperplasia cases of eight patients and oral leukoplakia cases of 24 patients using topical ALA-PDT (20% gel). A complete regression of OVH was obtained and partial response of oral leukoplakia after eight treatments twice a week [1]

Oral Lichen Planus

The following are second generation photosensitizer:

Lichen planus is a relatively common chronic inflammatory mucocutaneous disease. Although the cause is not well known, T cell- mediated autoimmune phenomena are involved in the pathogenesis of lichen planus [14]. The reported frequency of malignant transformation varies greatly from 0.4% to more than 5% over a period of 0.5 to more than 20 years. Treatment options for oral lichen planus are numerous, including topical, intra lesional and systemic corticosteroids, topical cyclosporine and tacrolimus, topical and systemic retinoid, however, outcomes are often disappointing. So searching for new treatment modalities seems quite rational. The exact mechanism of action of PDT is unclear. It has been suggested that PDT may have immunomodulatory effects and may induce apoptosis in the hyper-proliferating inflammatory cells, which are present in psoriasis and lichen planus. This may reverse the hyper- proliferation and inflammation of lichen

planus [14]. Kirby et al. reported one case of hypertrophic lichen planus on the penis treated using ALA-mediated PDT twice in a week. The lesion had completely resolved after 4 weeks. At six-month follow-up there was no recurrence. Aghahosseini et al. in 2006 conducted a study in 13 patients with 26 oral lichen planus lesions with methylene blue-mediated photodynamic therapy (MB-PDT). Patients were instructed to gargle a 5% methylene blue solution in water for 5 minutes and irradiation was performed by laser light 10 minutes later. Lesions were evaluated preoperatively and postoperatively and at follow-up sessions by changes in sign and symptom (pain) scores and size of lesions. Improvement in sign scores was achieved in 16 lesions and four reticular oral lichen planus lesions disappeared completely. There was a statistically significant decrease in sign and symptom scores 1 week after treatment and at follow-up sessions up to 12 weeks. Average reduction in size of lesions was 44.3%. They concluded that MB-PDT seems to be an effective alternative treatment for control of oral lichen planus [14].

Aghahosseini et al. in 2006 conducted a study at the clinic of Iranian center for medical laser in which two patients with five oral lichen planus lesions were treated using topical PDT mediated by methylene blue (MB-PDT). Ten minutes prior to laser irradiation, patients gargled MB for 5 minutes. A diode laser (632 nm) was used as light source. The patients were followed-up on sessions 3, 7, 15 days and 1 to 9 months after PDT. Clinical improvement was achieved in 4 lesions. Two lesions showed complete remission, and another two lesions had about 50% clinically improvement 3–9 months after a single session of PDT. No response was detected in one lesion. MB-PDT seems to be an effective alternative treatment for control of oral lichen planus [15].

Oral Squamous Cell Carcinoma

The following are third generation photosensitizer:

Squamous cell carcinoma of larynx and oral cavity may be treated effectively with single-modality therapy. The preferred treatment modality is surgery for early-stage oral cancer and radiotherapy for early laryngeal cancer. However, irradiation and surgery may result in long-term morbidity. The limitation of surgical resection in the oral cavity and larynx is that it leads to the removal of vital functional tissue, such as part of the tongue in the oral cavity, which may affect speech and swallowing [16].

Radiotherapy to the oral cavity often results in long-term morbidities, such as xerostomia, dysphagia, loss of dentition, and risk of osteoradionecrosis. An optimal treatment for moderate to severe dysplasia and early carcinomas of the oral cavity and larynx would be one that is safe, effective, repeatable, minimally invasive, and devoid of permanent sequelae is the photodynamic therapy [16].

Advantage of photodynamic therapy over conventional treatment modalities in head and neck carcinoma:

The main advantage of PDT for dysplasia and early

carcinoma of the larynx is the ability to preserve normal endolaryngeal tissue while effectively treating the lesion. This results in preservation of laryngeal function and voice quality. It may be performed in an outpatient setting using a single non-invasive light activation treatment, requiring a short duration for therapy. Photodynamic therapy can be repeated without the additional permanent functional laryngeal impairment that can occur with repeated conventional laser surgery or cordectomy. Photodynamic therapy spares the tissue architecture, providing a matrix for regeneration of normal tissue by leaving sub epithelial collagen and elastin intact, and spares non-cellular supporting elements. A further more important positive aspect of PDT is that it can be repeated [16].

Fan et al. in 1996 conducted a study in which 18 patients with histologically proven premalignant and malignant lesions of the mouth were sensitized with 60 mg/kg ALA by mouth and treated with laser light at 628 nm (100 or 200 J/cm²). They concluded that PDT using ALA for dysplasia of the mouth produces consistent epithelial necrosis with excellent healing and is a simple and effective way to manage these patients. Results in invasive cancers are less satisfactory; mainly because the PDT effect is too superficial with current treatment regimens using ALA as the photosensitizing agent [17]. Colin Hopper (2000) stated that PDT is a minimally invasive treatment with great promise in malignant disease. It can be applied before, or after, chemotherapy, ionizing radiation, or surgery, without compromising these treatments or being compromised itself. Unlike radiotherapy and surgery, it can be repeated many times at the same site. Response rates and the durability of response with PDT are as good as or better than, those with standard loco regional treatments [18]. Schweitzer (2001) conducted a study to determine the efficacy of Photofrin mediated photodynamic therapy. Ten patients with early stage squamous cell carcinoma of oral cavity and oropharynx and 10 patients with squamous cell carcinoma (SqCCA) of the larynx were treated. They concluded that Photofrin-mediated PDT provides a surgical oncologic modality for potentially curative treatment of early stage oral cavity and laryngeal malignancies with minimal side effects [19].

Verrucous carcinoma

The following are fourth generation photosensitizer:

Chen et al. (2005) conducted a study and showed that a new topical 5-aminolevulinic acid-mediated photodynamic therapy (ALA-PDT) protocol using a light-emitting diode (LED) light source is an effective and successful treatment modality for five cases of oral verrucous hyperplasia and one case of verrucous carcinoma. They concluded that complete regression of oral verrucous hyperplasia lesions can be achieved by less than six treatments of topical ALA-PDT once a week. Although the response of oral leukoplakia lesions to the topical ALA-PDT is not as good as the response of oral verrucous hyperplasia lesions to the same therapy, all

oral leukoplakia lesions can have at least PR after eight treatments with the topical ALA-PDT twice a week. In addition, oral leukoplakia lesions treated twice a week have a significantly better clinical outcome than oral leukoplakia lesions treated once a week [20]. Chen et al. (2005) tested the efficacy of this new treatment protocol of ALA-PDT for an extraoral verrucous carcinoma lesion at the right mouth angle and an intraoral verrucous carcinoma lesion at the right buccal mucosa of a 56-year-old male areca quid chewer and smoker. The extra oral tumor was cleared after six treatments of topical ALA-PDT and the intraoral tumor showed complete regression after 22 treatments of topical ALA-PDT. No recurrence of the verrucous carcinoma lesion was found after a follow-up period of six months. They suggested that new topical ALA-PDT protocol composed of multiple three-minute fractionated irradiations with a light emitting diode (LED) red light at 635 +5 nm for a total of 1000 s after topical application of 20% ALA for 1.5 or 2 h can be used successfully for the treatment of oral verrucous hyperplasia [21, 22].

CONCLUSIONS

Photodynamic therapy (PDT) is an alternative modality for the treatment of certain cancers. The success of PDT lies in the right combination of the parameters like photosensitizers and specific wavelength light and the application of PDT needs careful monitoring. At present, PDT is most successful for the superficial lesions of the epithelium such as basal cell cancer, microinvasive and intraepithelial dysplasias. The maximum depth of necrosis achieved by PDT is at around 1 cm hence it is not suitable for lesions greater than 1 cm diameter. Treatment of bulky tumors may be possible with interstitial PDT which involves insertion of fiber-optics in the tumor bed. In addition, PDT can be used intra-operatively just after the surgical removal of cancers which may help elimination of the residual tumor cells. During the past 30 years, PDT has been employed in the treatment of many tumor types, and its effectiveness as a curative and palliative treatment is well documented. “But why is its role in other disciplines still marginal?” In general, it is difficult to persuade clinicians to use a new technique when standard treatments yield a high response rate. Although lasers have become much less expensive, the setup of a new PDT centre remains costly. For the establishment of PDT in the routine clinical practice for the treatment of cancers, well designed preclinical studies and clinical trials are required.

Author Contributions

Nagalaxmi Velpula – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising

it critically for important intellectual content, Final approval of the version to be published

Kotya Naik Maloth – Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Srikanth Kodangal – Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Vani Chappidi – Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

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Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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