ABSTRACT

Photodynamic therapy is a new modality of therapy being used for the diagnosis and treatment of many tumors. It is now being increasingly used for skin tumors and other dermatological disorders. With its range of application it is certainly the therapy of the future. Its mechanism of action is by the Type II photo-oxidative reaction. The variables are the photosensitizer, the tissue oxygenation and the light source. It has been used to treat various disorders including Bowen’s disease, actinic keratoses, squamous cell carcinomas, basal cell carcinomas, and mycosis fungoides. The side-effects are fortunately mild and transient. Newer photosensitisers like methyl aminolevulinate hold a lot of promise for better therapy.

Key Words: Photosensitizer, Light source, Aminolevulinate

HISTORY

The use of sunlight for the treatment of various skin disorders (heliotherapy) was known to ancient Indians and Greeks. In the modern era, Oscar Raab, a German medical student first reported the death of Paramecium caudatum (a protozoan) after light exposure in the presence of acridine orange in the year 1900. His professor, von Tappeiner, coined the term “photodynamic” to describe oxygen-consuming chemical reactions in vivo. Von Tappeiner and Jesionek (a dermatologist), in 1904, used topical eosin and visible light to treat skin tumors, condyloma lata and lupus vulgaris.

DEFINITION

Photodynamic therapy (PDT) is a treatment modality involving administration of a photosensitizing compound, accumulation of the sensitizer molecules in the target cells followed by selective irradiation of the lesion with visible light. The drug and light are individually non-toxic, but in combination destroy tissues.

MECHANISM OF ACTION

The efficacy of PDT depends on all the following mechanisms which are inter-linked: direct cytotoxicity, vascular damage, inflammation and immune host response.

Direct cytotoxicity: In PDT absorption of a light photon by the sensitizer causes its promotion from the ground state to the extremely unstable short lived excited singlet state. The singlet excited photosensitizer emits fluorescence and decays back to the ground state or to the longer lived triplet excited state. Interaction of the triplet sensitizer with surrounding molecules results in photo-oxidative reactions (POR) that release singlet...
oxygen resulting in phototoxicity. Lipid peroxidation leads to cell membrane defects, which result in cell lysis [Figure 1]. Damage to mitochondria, lysosomes or endoplasmic reticulum occurs depending on the location of the photosensitizer in the cell. As most photosensitisers do not localize in the nucleus, nuclear damage is not an important factor of PDT-mediated cytotoxicity.

Vascular injury: Vascular injury is important in tumor destruction mediated by PDT. Vascular endothelial damage leads to platelet and polymorphonuclear leucocyte activation that releases pro-aggregatory agents. These events result in arteriolar constriction, venular thrombosis and blood flow stasis causing indirect tumor cell kill from nutritional deprivation.

Inflammatory response: Degradation of phospholipids occurring after photo-oxidative damage of cell membrane and impairment of vascular functions results in the release of various inflammatory mediators. This leads to accumulation of immune effector cells like macrophages and neutrophil granulocytes. Degranulation of neutrophils and release of toxic oxygen radicals, lysosomal enzymes and chemotactic agents contribute to the destruction of the tumor tissue and sustain the damage by attracting further immune cells. Establishment of immunological response against the treated malignancy leads to generation of tumor-specific immune cells that appear to be directed against both strongly and poorly immunogenic cancer types.

Host immune response: Thus mobilization of the host to participate in the tumor ablation process is a unique feature of PDT and is an advantage over conventional anticancer therapy. Use of monoclonal antibody-sensitizer conjugates results in greater selectivity and higher complete response rates, enhancing the antitumor properties of PDT.

Factors affecting efficacy of PDT
The variables in PDT are:
1. Photosensitizer
2. Tissue oxygenation
3. Light source

Photosensitisers
Photosensitisers that are under various stages of investigation for photodynamic therapy are listed in Table 1. An ideal photosensitizer should be chemically pure, have capability of localizing specifically in neoplastic tissue, should accumulate maximally in tumor in short time, and have a short half-life and rapid clearance from normal tissues. It should activate at wavelengths with optimal tissue penetration, have a high quantum yield for singlet oxygen generation, should lack dark toxicity and should be effective on topical application for dermatological uses.

Systemic PDT
Initially, after systemic administration, photosensitizing compounds are taken up by most normal and malignant cells, but are retained longer in tumor and rapidly proliferating cells. This may be due to increased blood vessel number and permeability and poor lymphatic drainage in neoplastic tissue. In fact, many normal tissues, especially the reticuloendothelial system have greater affinity for photosensitisers than tumor tissue.

The drug is activated by light corresponding to the absorption spectrum of the compound. The depth of tissue penetration depends on the wavelength of this absorption spectrum. Light of 630 nm wavelength penetrates 5 mm into tissues while that between 700-800 nm penetrates to 1-2 cm depth. Light at 850 nm does not yield enough energy to produce sufficient
Hematoporphyrin derivative (HpD) was the first systemically studied photosensitizer for clinical PDT. Photofrin (porfimer sodium) has enhanced photosensitizing properties and consists of non-metallic oligomeric porphyrins viz. a mixture of ethers and esters of porphyrin. This is activated at 630 nm. At this wavelength there is no penetration beyond 5 mm, hence lesions may not be effectively treated. The main disadvantage is cutaneous accumulation and slow clearance from skin leading to long lasting cutaneous photosensitivity, as long as 4-6 weeks.

Systemic ALA is used to treat gastrointestinal, bronchopulmonary and cerebral tumors. ALA-based PDT can be potentiated with the use of additive compounds to inhibit or induce certain enzymes of the heme synthesis pathway. 1. Desferrioxamine enhances ALA-induced protoporphyrin IX (PpIX) accumulation. 2. Combination of DMSO and EDTA with ALA increased PpIX production and enhanced the complete response rate of nodular basal cell carcinomas.

**Topical PDT**

Topical PDT depends on protoporphyrin IX (PpIX) formed endogenously in tissue after application of d-aminolevulinic acid (d-ALA). Topical application of d-ALA subverts the negative feedback effect on the heme pathway and leads to accumulation of endogenous PpIX in significant levels. Kennedy et al first used ALA-PDT for various malignant skin lesions. The main advantage of topical ALA-PDT is the absence of generalized photosensitivity. Limitations of topical ALA are that it is an unstable hydrophilic molecule, has poor penetration depth and consequent requirement of long application times, has low tissue selectivity and may cause porphyrin to accumulate in distant sites.

Methyl aminolevulinate cream is currently being investigated clinically. Its advantages are that it is a stable lipophilic molecule, has greater and faster penetration as well as a greater selectivity for neoplastic cells and shows no systemic uptake.

**Tissue oxygenation**

Experimental attempts at improving PDT effectiveness by manipulating tumor oxygen content like subjecting the tissue to hyperbaric oxygen have been made. However, this has no place as yet in clinical PDT.

**Light sources**

The therapeutic window for PDT is between 600 nm and 1200 nm as light of wavelength below 600 nm is absorbed by hemoglobin in the tissues and that above 1200 nm is absorbed by water. Light sources may be coherent (lasers) or incoherent. Laser beams can be launched via fiberoptic cables and delivered into internal tumors via implanted fibers.

When porphyrin photosensitisers are used, lasers of wavelength around 630 nm are required to match their absorption maxima. Argon pumped dye lasers (630 nm) or gold vapor laser (628 nm) are traditionally used but are expensive and need regular maintenance. More convenient is the Nd-YAG laser (690-1100 nm) for the non-porphyrin photosensitisers.

Incoherent sources of light used have been slide
Table 2: Potential uses of PDT in dermatology

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<thead>
<tr>
<th>Oncologic</th>
<th>Non-oncologic</th>
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<tr>
<td>Actinic keratoses</td>
<td>Psoriasis vulgaris</td>
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<tr>
<td>Bowen’s disease</td>
<td>Human Papilloma Virus associated dermatoses viz.</td>
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<td>Superficial squamous and basal cell carcinoma (BCC)</td>
<td>Epidermodysplasia verruciformis</td>
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<td>Nevoid BCC (Gorlin’s) syndrome</td>
<td>Condyloma acuminata</td>
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<td>Keratoacanthoma</td>
<td>Permanent hair epilation</td>
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<td>Kaposi’s sarcoma</td>
<td>Alopecia areata</td>
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<td>Cutaneous metastases</td>
<td>As an antibacterial in wound healing and acne</td>
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<td>Cutaneous T cell lymphoma</td>
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<td>Tumors in Xeroderma pigmentosum</td>
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<td>Actinic cheilitis</td>
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Basal cell carcinoma: PDT is safe and effective for the eradication of superficial BCCs. However, surgical excision, curettage with electro-dessication, radiotherapy, liquid nitrogen and Mohs micrographic surgery are superior to PDT in terms of long-term recurrence rates. PDT is a good alternative for those medically unfit to undergo surgery or previously treated with radiation therapy. PDT is ideal where surgery of extensive lesions could lead to cosmetic disfigurement or functional impairment. PDT is not effective in sclerosing BCC, has shown only moderate results in the pigmented variety, but is very valuable for recurrent BCC of Gorlin’s syndrome. “Photodynamic diagnosis” i.e. delineating the actual borders of BCC using PDT helps in ensuring complete surgical removal of tumors. However, the morpheiform variant of BCC cannot be treated with PDT probably due to insufficient porphyrin synthesis and inadequate penetration of light.

Squamous cell carcinoma: Systemic and topical PDT is a useful diagnostic and adjunctive therapeutic modality in SCC. Diagnostically it helps delineate the exact extent of the tumor.

Kaposi’s sarcoma: Studies to date have shown that response rates with PDT are equal to those with other therapeutic modalities in Kaposi’s sarcoma.

Mycosis fungoides: Various clinical studies have shown encouraging results for cutaneous lymphoproliferative malignancies with photodynamic therapy. However, there are no controlled trials yet and treating lesions locally would probably not prevent new lesions from coming up. However PDT can be a useful additional treatment modality for patients with therapy-resistant lesions of cutaneous T-cell lymphoma.

Malignant melanoma: The melanin content of melanoma markedly reduces penetration of light. Less pigmented lesions show better results with PDT. However, PDT is not really an acceptable modality for melanoma in view of its high propensity for rapid spread.

Skin metastases: Palliative PDT of cutaneous metastatic breast carcinoma has been one of the earliest
dermatological applications in the history of PDT. The conclusion from various studies is that PDT is helpful to palliate initial small metastases of breast cancer but is not suitable for the management of advanced or inflammatory carcinoma due to low response rate and complications like severe pain and extensive cutaneous necrosis.

Systemic PDT has been successfully used in the treatment of extramammary Paget’s disease resistant to conventional therapy,[18] severe lip dysplasia due to nicotine abuse,[2] and actinic cheilitis.[30]

Non-oncologic uses: In psoriasis of the chronic plaque type, both systemic and topical PDT have shown results, in some cases equivalent to results with dithranol.[2,31] Though no controlled studies have been done, topical 10% ALA ointment applied for 5 hours followed by irradiation with 25 J/cm² from an incoherent light source showed clearing of chronic plaque psoriasis.[32] Verrucae vulgaris, including recalcitrant ones, laryngeal papillomas and condyloma acuminata have responded well to PDT.[2,33,34] PDT has also been used for the treatment of recalcitrant and HIV-associated molluscum contagiosum.[35,36] PDT appears to be an efficient modality for cutaneous vascular malformations with excellent cosmetic results.[2] Topical HpD and long wave ultraviolet light have led to growth of coarse terminal hair in areas of patchy alopecia areata.[2] Hirsutism responded to PDT with the advantage that hair follicle damage was highly selective and did not damage the adjacent dermis.[2]

COMBINATION OF PDT WITH OTHER MODALITIES

PDT can be effectively combined with surgical debulking of tumors to make therapy more effective. In combination with adriamycin and mitomycin, it leads to additive anti-tumor effects.

Adverse effects
The side-effects of PDT are relatively mild and transient.
1. Burning pain, stinging or itching restricted to the illuminated area may be seen during light exposure. Rarely, the pain persists for a few hours after the end of treatment. Local anesthesia or premedication with benzodiazepine may help control the pain.

2. Erythema and edema of the treated area may occur after light exposure and may be treated by mild topical corticosteroids.
3. After PDT, there is crusting, scaling accompanied by pruritus and then healing takes place by 2 to 8 weeks. Urea-containing ointments help resolve dry crusts and accelerate re-epithelialization. A light overdose may lead to blistering, ulceration and excessive necrosis.
4. Systemic photosensitisers can cause long-lasting generalized cutaneous photosensitivity and phototoxicity manifesting as burning, stinging, erythema, edema and bullae formation. Sunlight, bright spotlights, photocopy machines, photographic flashlights, medical examination lights and operation lamps are to be avoided. Ordinary indoor light is safe and may help in photo-inactivation of residual drug molecules in the skin.
5. Photophobia and ocular discomfort may also occur.
6. Residual hyper and hypopigmentation have been reported.
7. Systemically administered HpD may cause vomiting, nausea, metallic taste and liver toxicity.
8. Systemic PDT is hazardous for porphyria patients and since porphyrins cross the blood brain barrier, it may precipitate neurological symptoms of acute intermittent porphyria.
9. Following PDT, exacerbation of SLE, photo-Koebner reaction leading to reactivation of psoriasis and malignant melanoma have been reported.

However, the merits of PDT outweigh by far its demerits in most cases and it is going to be an important part of the dermatologists’ armamentarium in the future. For better therapeutic efficacy with PDT more clinical, biochemical and physical research will be needed.

REFERENCES