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Photodynamic therapy (PDT), based on eradication of target cells via a photosensitising agent and light of an appropriate wavelength, is a novel approach for the treatment of cancers. Preclinical and clinical studies carried out in many centres have shown that PDT is a successful technique for the treatment of certain cancers. PDT 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 PDT without going into the details of its use in specific branches. [Turk J Cancer 2002;32(3):83-91]

Key words: Photodynamic therapy, cancer, photosensitiser, laser

Photodynamic therapy (PDT) is a promising new approach for the treatment of cancers. It is based on eradicating target cells by the interaction between light and a light-activated compound (termed the photosensitiser) in the presence of oxygen.

The discovery of PDT dates back to in the beginning of 1900's. A medical student Raab (1) observed by chance that the dye, acridine orange in the presence of light was toxic to protozoa. In the following years, it was shown that basal cell cancer cells could also be killed when exposed to eosin and light for several weeks (2). No significant subsequent studies on the photodynamic effect on tumors were reported until 1942 by Auler and Banzer (3), who injected tumor-bearing animals with haematoporphyrin (a substance processed from human blood) and exposed them to a quartz-halogen lamp, observing necrosis and fluorescence of tumors. Following the purification of haematoporphyrin to form a haematoporphyrin derivative (HpD) which has an improved photosensitising activity and the advent of the laser by Maiman in 1960, more widespread therapeutic applications of PDT were developed (4,5). In 1978, Dougherty et al. (6) demonstrated a partial or complete response in tumors in humans when HpD and light at 630 nm were used together, which stimulated further studies on PDT. Development of endoscopic devices offered a new opportunity for the treatment of cancers in less accessible areas such as the bladder, lung and oesophagus, with Hayata et al. (7) being the first to use fiberoptic laser exposure to treat early bronchial cancer with PDT in 1982.

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Numerous photosensitisers have been developed and many are currently under investigation. The purified active component of HpD is enriched in dihaematoporphyrin ether (DHE). It has become available under the commercial name of Photofrin which was the first substance to receive regulatory approval for PDT applications (8). Promising results have been reported on PDT on early malignant lesions in many disciplines including maxillofacial, skin, pulmonary, gastrointestinal and genitourinary systems (9-26).

PDT has several advantages over conventional approaches (surgical excision, radiotherapy and chemotherapy). PDT may be non-invasive, is non-ionising, and is a repeatable technique with no cumulative effect. The effect produced by PDT is minimal on the connective tissue hence better wound healing and esthetic results can be obtained. The function of the organs can also be preserved following PDT. Illumination of the less accessible areas can be achieved by the use of fiber optics. PDT can be applied under local anesthesia and sedation however some degree of pain is expected after PDT and analgesics may be required. The cost of this treatment is less expensive compared to the other conventional modalities.

The photochemical basis of PDT

When a photosensitiser absorbs light energy of an appropriate wavelength, in the presence of oxygen, a series of photochemical reactions occur. Following the absorption of light, the photosensitiser molecule transfers from the ground state to the excited singlet state which has high energy but an extremely short lifetime. From this excited singlet state, the molecule can then may follow two pathways: The molecule may decay back to its ground state emitting fluorescence light. The fluorescence properties of some sensitisers have been used diagnostically for detecting the sensitiser in tissues and for visualising tumor localisation (27-29). However for the photodynamic effect to take place, the molecule must convert to a triplet state which has a lower energy, but has a longer lifetime than the singlet state (1 μsec-10s). The triplet state molecule transfers its energy to oxygen molecules present in the tissues to generate singlet oxygen. Singlet oxygen is highly reactive and believed to be the primarily cytotoxic species which induce tissue damage in PDT. The excited triplet photosensitiser can also interact with a biomolecule or solvent molecule and produces radical forms of the substrate or photosensitiser, which can then react directly with oxygen to produce active species such as hydroxyl radicals, hydrogen peroxide and superoxide anions (30-32).

The photobiological effects induced by PDT

Singlet oxygen has a short life-span (0.01-0.04 ms) and a diffusion of approximately 0.01-0.02 μm and therefore the sites of initial cell damage are closely related to the localisation of the photosensitiser (31). Most of the photosensitisers used in PDT are lipophylic and accumulate in the cytoplasmic membrane. Lipid peroxidation and protein damage in the plasma membrane lead to an increased permeability and inhibition of the cell nutrient transport (33-35). In addition, photosensitisers have an affinity to the membrane of the intracellular organelles. Disruption of mitochondrial enzymes are thought to be responsible for mitochondrial damage (36). Photosensitisers localised in

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lysosomes cause the release of hydrolytic enzymes into the cell interior upon light exposure (37). Degradation of nucleic acids have been observed in response to cytotoxic damage. DNA repair enzymes are also extremely sensitive to reactive species (38). However, it is thought that PDT has a very low mutagenic activity and does not have carcinogenic potential.

Such damage produced in the cellular structures result in necrosis of the tissues. In addition, cell lines exposed to PDT have been shown to exhibit cell death with features of apoptosis (39,40). Although not fully understood, it has been suggested that apoptosis occurs when low doses of the sensitiser and light were used whereas higher doses cause lysis of the cells.

Although the cytotoxic species have direct effect on the tumor cells, the most significant destructive effect of PDT appears to be mediated by vascular damage both on the tumor bed and in the surrounding normal tissues (41). Arterial endothelial cells are particularly susceptible to photodynamic destruction because of the high oxygen tension. It has been shown that poorly vascularised tissues are not as sensitive to PDT as the tissues with good blood supply (42,43).

PDT has also been shown to induce an inflammatory reaction. One of the early effects of PDT is a massive inflammatory response characterised with neutrophil infiltration to the tumor bed. An increased tumor-specific T cell activation can also be observed following PDT. In addition, it has been claimed that the anti-tumor effect is enhanced by the stimulation of numerous potent mediators (such as cytokines) and by the invasion of the defense cells into the tumor bed (44,45).

Erythema and edema are the early clinical signs following PDT. Aggregated platelets in microvascularity shortly after irradiation was shown in experimental tumor models. Subsequently, a transient vasoconstriction followed by vasodilatation, stasis and hemorrhage was observed (46). However, the subendothelial collagen and elastin are preserved. The vascular collapse is irreversible and leads to hypoxia and necrosis of the tissues (14,47,48). The necrosis is not only limited to the tumor tissue but also includes the adjacent normal tissue exposed to the laser light. However, adjacent normal tissues regenerate satisfactorily and (due to limited damage to the connective tissue fibers) with minimal tissue loss and preservation of function (14,47,48).

Clinical photosensitisers

A variety of photosensitisers in conjunction with light of various energy doses have been used in the PDT studies. DHE under the commercial name of Photofrin has been the most commonly used photosensitiser and called as the 'first generation' (13,14,20-22,24,25). The depth of necrosis achieved by Photofrin mediated PDT is about 0.5 cm. It has no systemic toxicity other than prolonged photosensitivity (for approximately 4-8 weeks). It may cause severe sunburn-type reactions as a result of exposure to direct sunlight. So called 'second generation' sensitisers are being investigated to improve the effectiveness of PDT. 5-aminolaevulinic acid (5-ALA) is the metabolic precursor of protoporphyrin IX (PpIX) in the biosynthetic pathway to haem. After administration, 5-ALA metabolises into PpIX which can act as an endogenous sensitiser. The depth of necrosis produced by 5-ALA-induced PDT is generally

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not more than 1.5 mm and therefore it is used for the treatment of superficial skin cancers, especially basal cell carcinoma and dysplasias in the oral cavity, but is not suitable for invasive cancers (10,16-18). The advantage of this photosensitiser over HpD is that 5-ALA-induced PpIX is cleared from the body more rapidly, so duration of the period of skin sensitivity beyond 2 days is avoided. Meso-tetrahydroxyl tetraphenyl chlorin (m-THPC) is effective at low drug and light doses. m-THPC-induced PDT offers a deeper tumor destruction (1 cm) and larger tumors (up to stage T1 tumors) can be effectively treated. Cutaneous photosensitivity is around 6 weeks at the most and some scarring on healing can be expected (11,19). Phthalocyanines (synthetic porphyrin analogues) are not retained in the skin so long as porphyrins therefore, less cutaneous sensitivity is experienced (49). Clinical studies on the effectiveness of phthalocyanines are underway.

Light sources

Any light source can be used for PDT as long as it has the required spectral characteristics. The light source must emit light of an appropriate wavelength, corresponding to the absorption maximum of the sensitiser and must have sufficient energy to activate it. Since their development, lasers have become the standard light source for most PDT applications, owing to their superior properties over ordinary light, mainly their high energy content, their monochromacity and the fact that the light emitted can be guided via optical fibers. The conventional light sources (such as the xenon light) has a very wide spectrum. Appropriate wavelengths can be obtained by filtration of the emitted spectrum but this may also eliminate the desired beams and reduce the intensity. The wavelength that activate the photosensitisers available currently is around 630-660 nm which gives red light. Various light sources have been used for PDT. The tunable dye laser systems such as argon or copper vapour-pumped dye lasers have been commonly used until recently. Light-generating devices required for PDT have been moving into the field of cheaper, less complicated, small, portable and simple to use light sources such as diode lasers and non-coherent light sources.

The absorption of laser light by tissues is wavelength-dependent and tissue penetration is greater at longer wavelengths. The red light can penetrate for about 1 cm, intensity of which is reduced by a factor of ten compared to the intensity at the surface. Penetration is almost doubled when near infrared light (700-850 nm) is used, thus new photosensitisers that absorb the light from this range have been under development.

Clinical application of PDT

Administration of the photosensitisers may be oral, intravenous or topical. Although the accumulation is higher in the neoplastic tissues, the photosensitiser is also retained in the normal tissues with varying concentration. The extent of accumulation in the tumor and normal tissues depends on the specific photosensitiser, the route of administration and the type of the tissue (50-53). For instance, on intravenous Photofrin administration the tumor-normal tissue ratio of the photosensitiser was found to be 28:1 in the brain, 2-3:1 in the intestines and pancreas (51). The difference between the tumor and the normal

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tissue concentration reaches to maximum in a certain period after the administration of the photosensitiser (e.g., 2-3 days for Photofrin) immediately after which time the light is exposed. The light exposure time depends on the power of the laser source and the energy dose used. For instance, when 100 mW diode laser is used and 1 cm^2 area is exposed to 100 J/cm^2 of light the irradiation time then will be 16 minutes. The commonly used photosensitising compounds and the treatment parameters are given in table 1.

Table1
The commonly used photosensitisers and the treatment parameters

	Drug dose	Drug-light interval	Light wavelength and energy dose
DHE (Photofrin)	2-5 mg/kg (iv)	24-72 h	630 nm, 100-200 J/cm^2
5-ALA	Topical or oral	4 h	630 nm, 100-200 J/cm^2
m-THPC (Foscan)	0.3 mg/kg bolus injection	72-96 h	652 nm, 8-20 J/cm^2

Although the photosensitiser is accumulated in the tumor more than the normal tissues, the necrosis produced by PDT includes the adjacent healthy tissue as well as the tumor bed. A more selective effect can be obtained by directing the light to the target area. The response of the adjacent healthy tissues to PDT is also important for the success of the treatment. PDT has little effect on the collagen and the cartilage which is a great advantage for the continuity of the structures and mechanical properties such as internal pressure and resistance to stress are preserved. PDT may particularly be suitable for the hollow organs including trachea, intestine and bladder. The risk of perforation and collapse of airways may be smaller in PDT compared to the other treatment modalities.

The side effects of the PDT is, in general, few and transient. Some degree of pain and burning sensation may be experienced during irradiation. The most intense period is in the first 3 minutes after which time the pain is reduced gradually. The normal tissues heal by regeneration following PDT. Total healing of the area after PDT may take around 2-6 weeks. The most prominent side effect of PDT is the sensitivity to light. Depending on the photosensitising agent used, the light sensitivity may take from 4-5 hours (with 5-ALA) to up to 6 weeks (with Photofrin). During this period patients must be protected from the direct light, otherwise sun-burn type of reactions may occur. The light sensitivity may be reduced using tumor selective antibody-conjugated photosensitisers which may inhibit the accumulation of the photosensitiser in the healthy tissues hence reduce the side effects. It may also improve the effectiveness of the treatment (54).

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Depending on the specific area where PDT is applied few other side effects have been reported. Necrosis produced in the oesophagus may lead to fistula formation but it occurs less commonly compared to Nd:YAG laser surgery. (1% in PDT, 7% in the Nd:YAG laser use) (22). Endobronchial gelatinous secretion and oedema, stricture in oesophagus and reduction in the bladder capacity and dysuria have been reported with Photofrin-PDT (20,24,25). A reduction in the bladder capacity was observed when 5-ALA mediated PDT was used (26). These complications may be alleviated by modifying the parameters used in PDT. Moreover, leaving an interval between irradiations and fractionation of the total dose of light may be useful minimising the complications. Nseyo et al. (25) reported that low doses of repeated exposures decreased the symptoms and prevented the constricture formations in bladder. 5-ALA may cause tachycardia and hypotension in patients with cardiovascular problems (26).

Conclusion

PDT is an alternative modality for the treatment of certain cancers. The success of PDT lies in the right combination of the parameters employed and the application of PDT needs careful monitoring. Therefore, the clinician should have an extensive knowledge about the accumulation of the photosensitiser and the penetration and the absorption of the light through tissues.

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 (55).

The development of new photosensitisers that are activated by longer wavelengths (650-850 nm) and that produce minimal skin sensitivity together with more efficient light systems will increase the efficiency of PDT. Tailor-made PDT could be employed by selecting the appropriate photosensitiser according to the localisation and the size of tumor.

At present, there are several aspects requiring further evaluation in PDT and before it has established its place in the routine clinical practice for the treatment of cancers, well designed preclinical studies and clinical trials are required.

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