Photodynamic Therapy as a New Treatment Approach in Cancer

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Abstract:- Photodynamic therapy (PDT) is a treatment approach that uses a photosensitizer, and light, to kill cancer cells. The treatment consists of two stages. In the first stage, the photosensitizer is accumulated in cell, following topical or systemic administration. In the second stage, the sensitized tumor is exposed to light at a specific wavelength that is appropriate for the absorption spectrum of the photosensitizer. When this activated sensitizer transfers energy to molecular oxygen, reactive oxygen species are generated. Therefore, necrosis and/or apoptosis are induced in tumor cell. ROS can also stimulate the transcription and release of inflammatory mediators. There are different types of photosensitizer and each is activated by light of a specific wavelength. An ideal photosensitizer should be a pure compound, water-soluble to allow quality low manufacturing costs and good stability. It should have a absorption peak between 600 and 800-nm (red to deep red). Several photosensitizers are currently approved by the US Food and Drug Administration (FDA) to use with laser light. Wavelength determines how far the light can travel into the body. Therefore, each combination of photosensitizers and light wavelengths is used to treat different cancer types. PDT may also help by destroying the blood vessels around the cancer cells and by inducing the immune system to attack the cancer. Studies in clinic revealed that PDT, minimally invasive therapeutic procedure, can be curative particularly in early-stage tumors. It can help prolonged the life span and improve quality of life. To date, PDT is being tested in the clinic for use to treat cancers of the head and neck, brain, lung, pancreas, intraperitoneal cavity, breast, prostate and skin. The therapy can be used as an adjuvant therapy with conventional therapy such as surgery, radiation or chemotherapy. It can be concluded that PDT could be a promising cancer treatment modality with its curative potential.

Key-words:- Photodynamic Therapy, Laser, Photosensitizers, Cancer treatment

1 Introduction

Despite progress in medicine industry and medical technology, cancer still remains the most deadly disease in the World. It is necessary to find new therapeutic modalities [1]. Photodynamic therapy (PDT) provides a new and amazing modality because of its specificity and selectivity [2,3]. PDT can be used as an alternative method to treat various solid tumors, especially tumors in early stages, and as a palliative method in advanced cancers. It has also been used in combination as an adjuvant therapy with other therapies such as chemotherapy, surgery, radiotherapy, or other therapies such as anti-VEGF therapy (vascular endothelial growth factor), immunotherapy [1,4,5]. PDT has been shown to have good therapeutic effects in bladder, brain, colon, head and neck, esophageal, laryngeal, lung, prostate and skin cancers. PDT has also been good option in treatment of chest wall metastases in end-stage breast cancer patients, prolonging survival [1,6,7].

PDT involves 2 components, a photosensitizer (PS) and a light at specific wavelength. PS selectively localizes in malignant tissue and use of light activates PS to produce singlet oxygen, which results in tumor destruction [3,8,9]. In fact, use of a photosensitizer has been applied since ancient times in Greece, Egypt and India, where psoralen-containing plants were applied with light to cure psoriasis and vitiligo [6,10]. In 1903, the first use of photodynamic therapy was actualized by von Tappeiner and Jesionek who applied eosin topically to basal cell carcinoma [11].

In 1978, T. J. Dougherty and co-workers successfully applied this novel technique with hematoporphyin derivative (HpD) for cancer treatment in mouse mammary. Canada, Japan, France, the Netherlands, Germany and United States have clinically approved this treatment modality for selected malignancies [10]. After these successful trials, PDT has begun to attract attention [8].

2 Photo-sensitization and Photo-sensitizers

PS can be administered either locally, topically or systemically to a patient. Visible or near-infrared light is used to irradiate tumor site after biodistribution of PS. Therefore, photochemical reactions are induced via generating cytotoxic products that lead to cell death (Fig. 1) [15,16].

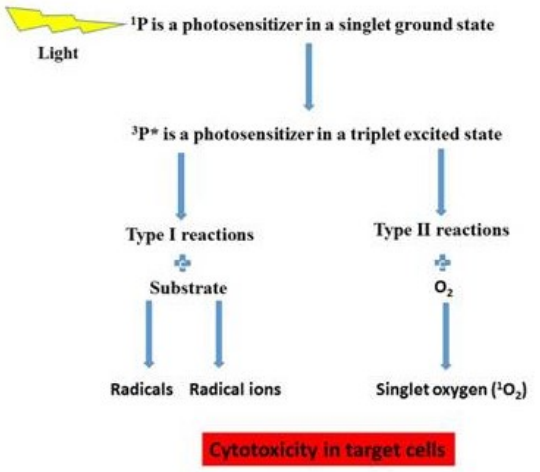

Figure 1. Photochemical reaction [adapted from 11,12,13].

Light exposure causes to transform photosensitizer from ground state (P_0) to the first excited state (P_1). The sensitizer is stable in the excited state. The triplet excited state (P_3) is a longer-lived state and P_1 undergoes P_3 through the intersystem crossing process. After this situation, two mechanisms occur simultaneously. First mechanism is called Type I. Hydrogen abstraction or electron transfer occurs between excited sensitizer and adjacent sensitizer molecule and ion radical forms. This radical reacts with ground state oxygen ($^3O_2$) and Reactive Oxygen Species (superoxide anion- $O_2^{-\bullet}$, hydrogen peroxidase- H_2O_2 and hydroxyl radical- $OH^{\bullet}$) are generated. Second mechanism is called Type II and energy from P_3 is passed to $^3O_2$ and then excites it to singlet oxygen ($^1O_2$). Type II which is a catalytic reaction, is the dominant process in PDT [8,14,16].

The singlet oxygen and other radicals react with biomolecules such as proteins, nucleic acids, and lipids. Damage of mitochondria, endoplasmic reticulum and cell membrane is induced by radicals. DNA damage may be enhanced by nuclear delivery of the photosensitizer [9].

Several sensitizers have been developed for clinical use. PDT with Photofrin was firstly approved by Food and Drug Administration (FDA) [8,16]. An ideal PS should meet at least some of the following criteria [5,16,17]:

- a commercially available pure chemical,
- low dark toxicity to humans and animals,
- strong photocytotoxicity,
- good selectivity towards tumor cells,
- longer wavelength allowing deeper light penetration,
- rapid elimination from the body,
- multiple administration routes (oral, intravenous, intratumoral or inhalational).
- water-soluble or soluble in a harmless aqueous solvent mixture
- stable shelf life

Although some PSs have all or some of these criteria, few PDT photosensitizers have received official approval around the world as seen below [2,5,16].

- Photofrin (630 nm; Axcan Pharma, Inc.), approved for Barrett's high grade dysplasia, cervical cancers, endobroncheal cancer, esophageal cancer, gastric cancer, papillary bladder cancer
- Levulan (prodrug of protoporphyrin IX, 630 nm; DUSA Pharmaceuticals, Inc.), approved for actinic keratosis
- Metvix (prodrug of protoporphyrin IX, 630 nm; PhotoCure ASA), approved for basal cell carcinoma
- Foscan (652 nm; Biolitec AG), approved for head and neck cancer
- Visudyne (693 nm; Novartis Pharmaceuticals) approved for basal cell carcinoma
- Hexvix, (380-450nm; Photocure ASA) approved for bladder cancer.

3 Light Sources

Light delivery is another key factor in determining PDT efficacy. Light tissue penetration is varied depending on wavelengths. Blue light has less penetration level, red and infrared lights penetrate more deeply. 600-1200 nm is called the optical window of tissue in PDT application. When light travels through tissue, different conditions are occurred such as reflection, scattering and absorption. Therefore light distribution is important in order to provide therapeutic effect of PDT in target tissue (Fig. 2) [1,2,3].

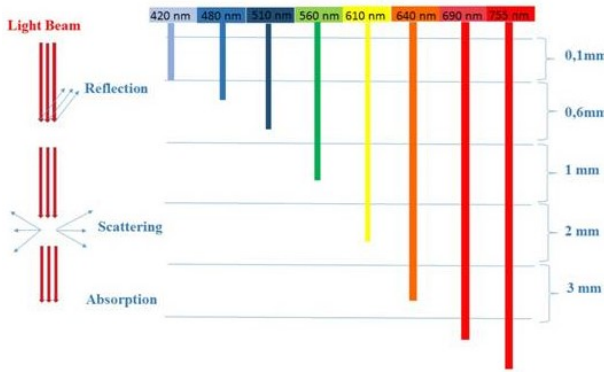

Figure 2. Penetration of different wavelengths in tissues [adapted from 1].

In order to apply PDT, various laser equipments have been produced for desired applications. Argon-dye laser sources that are widely used, generates a 630 nm light for activation of Photofrin. Metal vapor lasers also generate 628 nm wavelength but this system can be expensive and impractical. KTP: YAG/lasers have advantages such as low cost, easy to use and portability and this system generates a beam at 630 nm. The other system is Diode lasers that are approved by FDA to apply with Photofrin in esophageal and lung cancers. LED light is not laser light source, but this light also is used to make desired wavelengths at 630, 670 and 690 nm. Light sources may be also coupled with various devices such as fiber optics, cylindrical fibers and balloon catheters to irradiate cylindrical lumen including lung, esophagus and trachea [18].

4 PDT Mechanisms

Tumor cells can concentrate PS more than normal cells and normal cells can metabolise PS faster than tumor cells. When cells with PS are irradiated by light, phototoxicity is occurred. The photodynamic reaction of PDT result from three processes: tumor cell destruction by apoptosis, necrosis or autophagy, damage of tumor vascularization, and induction of immune system [14,19].

The concentration, properties and location of the PS, oxygen concentration, wavelength and intensity of the light, as well as the cell type specific properties may influence cell death mode. If higher light doses are applied, tumor cells are killed by necrosis because of severe mitochondria cell membrane disintegration and high intracellular Ca^{+2} levels. PDT also activates damage of Bcl-2 and related anti-apoptotic proteins and induces pro-apoptotic protein family by depending on photosensitizer type. Therefore apoptotic pathways can occur. Autophagy may be also stimulated and occur just before apoptosis depending on generated ROS type, use of photosensitizer type and lower light doses (Table 1) (Fig. 3), [1, 20].

Table 1. PDT effect on cell death mechanism

Loss of membrane integration	Necrosis
Bcl-2 damage, Cytochrome c release in mitochondria	Apoptosis
NFκB damage in cytoplasma	
Beclin-1 and mTOR activation	Autophagy

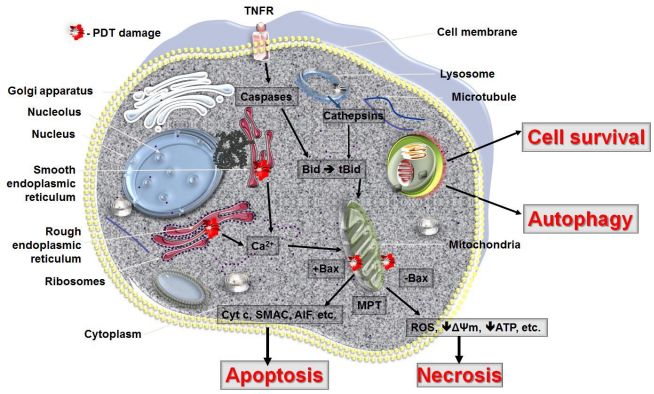

Figure 3. Effect of PDT in cell [20]

PDT can also induce damages of vascular walls in tumor region thus limiting oxygen supply to the tumor cells. Apoptosis or necrosis may be induced in blood vessel. Especially, endothelial cells that play crucial role in angiogenesis, are also target of PDT. Damage of endothelial cells leads to local inflammation, platelet aggregation. All these cascade of events also lead to induce immune reactions. Therefore, PDT have anti-angiogenesis properties to improve therapeutic outcomes. [1,6,19].

Immune system cells are suppressed in conventional therapies such as chemotherapy and radiotherapy, while PDT activates immune cells. When damaged tumor cells express heat shock proteins, they provide antigens to macrophages and neutrophils. These events may occur both local and distant lymphatic tissue nearby tumor region [6,19].

5 PDT Applications

Topical applications of porfimer sodium and aminolevulinic acid are generally used for skin tumors in PDT. The application is approved for treatment of actinic keratosis in European Union, United States and Canada. Several clinical studies have been reported that PDT has also useful therapy for basal cell carcinoma [1,6].

Head and neck carcinoma treatment is achieved by porfimer sodium-based PDT. Second-generation PSs such as ALA and temeporfin have been started to use for head and neck cancer treatment trials. Tumor mass reduction has been observed in these trials [1].

Success of prostate and bladder cancer treatment is also gained with PDT [1,22].

Several clinical trials revealed that PDT can be used as adjuvant therapy in patients with brain tumors as well as diagnostic tools [1].

PDT has advantages for patients with lung cancer if surgery is not feasible. PDT remains a very promising therapeutic approach in the treatment of non small cell lung cancer [1].

For digestive system tumors, PDT experience is limited [1].

PDT modality can also be an approach with good response in breast cancer in whom other treatments have failed [21].

6 Conclusion

It is obvious that we need new approaches to treat cancer. Photodynamic therapy can be promising approach in premalignant and malignant tissue. It can be used as combination with other therapies or it can be alternative therapy to provide therapeutic effetc. PDT can be repeatedly used if it is necessary. However we need further clinical applications of PDT.

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