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History and Basic Principles of Photodynamic Therapy Use in Ophthalmology

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ABSTRACT

Photodynamic therapy (PDT) is a therapy that uses drugs, called photosensitizers or photosensitizing agents, and a specific type of light. When photosensitizers are exposed to certain wavelengths of light, they produce oxygen that kills nearby cells. PDT is achieved by a photodynamic reaction induced by the excitation of a photosensitizer exposed to light. In the field of ophthalmology, PDT was approved for the first time about ten years ago for cases of age-related macular degeneration (AMD). Neovascular age-related macular degeneration (AMD) is a vision-threatening disease characterized by pathological macular neovascularization. After that, PDT was approved for use in choroidal neovascularization (CNV) cases in pathological myopia.3 This literature review aims to describe the history of PDT use and the basic principles of photodynamic therapy in ophthalmology.

1. Introduction

Photodynamic therapy (PDT) is a light-based therapy used for tumor ablation.[1] As practiced in oncology, photosensitive agents are applied and activated by specific wavelengths and energies of light.1 In the presence of oxygen, this light energy will cause photodynamic reactions that have cytotoxic and vasculotoxic properties.[2] This means that there are three essential components in PDT; photosensitizer, light source, and oxygen from tissues. In the field of ophthalmology, PDT was approved for the first time about ten years ago for cases of age-related macular degeneration (AMD).[2] Neovascular age-related macular degeneration (AMD) is a vision-threatening disease characterized by pathological macular neovascularization. After that, PDT was approved for use in choroidal neovascularization (CNV) cases in pathological myopia. This literature review aims to describe the history of PDT use and the basic principles of photodynamic therapy in ophthalmology.

Retina and choroid anatomy

The retina is the light-sensitive part of the eye located in the posterior segment of the eye.[3] The retina is an organized structure that provides visual information transmitted via the optic nerve to the visual cortex. The retina develops from the invaginated external optic cup starting at the end of the fourth week of fetal life. The adult eyeball has a diameter of about 22- 24.2 mm. A child's eyeball at birth is 16.5 mm in diameter and then reaches its maximum growth until 7-8 years. The retina occupies two-thirds to three-quarters of the posterior in the eyeball of this size. The total retinal area is 1,100 mm^2. The retina lines the posterior part of the eye, except the optic nerve, and extends circumferentially anteriorly 360 degrees at the ora Serrata. The retina is on average 250 μm thick,

thickest in the macula area with a thickness of 400 μm, thinning at the fovea at 150 μm, and thinner at the ora Serrata with a thickness of 80 μm. The retina is vascularized from the ophthalmic arteries (first branches of the right and left internal carotid arteries) and ciliary arteries (running with the optic nerve). The ciliary arteries provide vascularity to the outer and middle layers, including the outer plexiform layer, photoreceptor layer, outer nuclear layer, and pigment epithelial layer.[3,4]

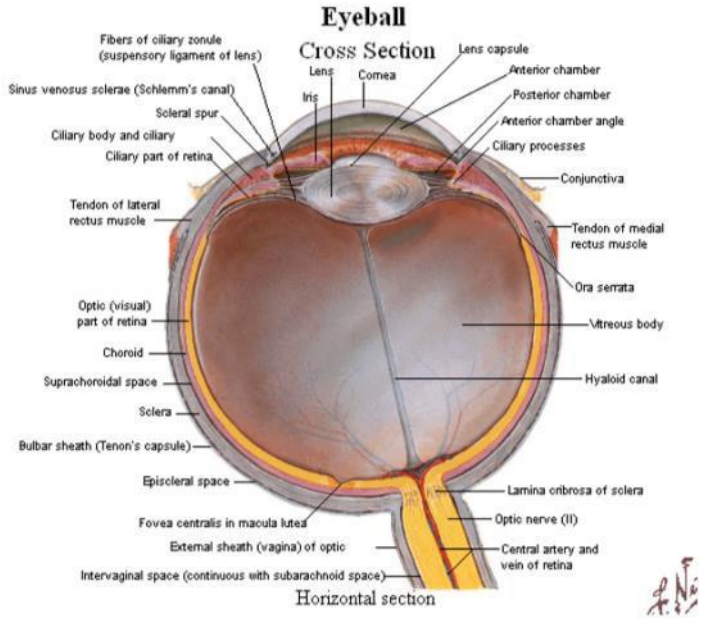

Figure 1. Retina anatomy[3]

Retinal histology and physiology

The outer surface of the retina is in contact with the choroid, while the inner surface is in contact with the vitreous body. The retina has ten layers, consisting of (from outside to inside); pigment epithelium, rods and cones, the external limiting membrane, the outer nuclear layer, and the outer plexiform layer, the inner nuclear layer, the inner plexiform layer, the ganglion cell layer, the nerve fiber layer, and the internal limiting membrane.[5]

The retina is the most complex part of the eye and is most sensitive to light. The retina has a photoreceptor layer containing rods and cones that have a role in capturing the light stimulus then transmits impulses through the optic nerve to the occipital visual cortex. Photoreceptors are arranged in the outer avascular retina of the retina, and many biochemical changes occur for the process of seeing. The composition of cone cells is more in the macula (fovea) and less in the periphery, while the density of rods is high in the periphery and few in the macula (fovea). Cone cells function to see color and during the day, so the fovea is responsible for color vision and light. Rod cells, containing the photosensitive pigment rhodopsin, function to see black and white at night so that the peripheral part is responsible for dark vision at night.[3,5]

The retina also has a neural layer consisting of bipolar cells, ganglion cells, horizontal cells, and amacrine cells. Bipolar cells are scattered in the retina and are responsible for connecting photoreceptor cells (postsynaptic rods and cones) and ganglion cells. Ganglion cells provide axons that join the optic nerve fibers to the brain. Horizontal cells are located in the outer plexiform layer and interconnect bipolar cells with other bipolar cells. Amacrine cells are located in the inner plexiform layer and link bipolar cells and ganglion cells.

In addition, the retina also has glial cells or supporting cells consisting of Muller cells, astrocytes, and microglia cells. Muller cells are located in the inner nuclear layer and provide an irregular thickness that extends to the outer

plexiform layer. Astrocytes are tightly enclosed in the nerve fiber layer of the retina. Microglial cells originate from the mesodermal layer and are not neuroglial cells.[3-5]

Choroid

The choroid is the posterior segment of the uvea, between the retina and the sclera. The choroid comprises three layers of choroidal blood vessels; large, medium, and small. The deeper the vessel lies within the choroid, the broader its lumen. The interior of the choroidal vessels is known as the choriocapillaris. Blood from the choroidal vessels drains through four vorticose veins, one in each posterior quadrant. The choroidal nerve is bounded internally by Bruch's membrane and externally by the sclera. The choroid is firmly attached posteriorly to the edges of the optic nerve. Anteriorly, the choroid joins the ciliary body.[5]

Photodynamic therapy (PDT)

Photodynamic therapy (PDT) is a therapy that uses drugs, called photosensitizers or photosensitizing agents, and a specific type of light.[1,6] When photosensitizers are exposed to certain wavelengths of light, they produce oxygen that kills nearby cells. PDT is achieved by a photodynamic reaction induced by the excitation of a photosensitizer exposed to light. This phenomenon was first reported by Raab et al. in 1990. In 1960 Lipson et al. reported on a hematoporphyrin derivative (HpD) by treating hematoporphyrin chloride with hydrochloric acid and sulfuric acid. The development of HPD became the basis of today's PDT. Dougherty reported the first PDT treatment of skin tumors with an argon dye laser in 1978.[7]

Kato and his colleagues began a pilot study of this treatment using Dougherty-provided HPD and an argon dye laser in canine lung cancer in 1978. These studies confirmed the effectiveness and safety of these methods. The authors performed bronchofiberscopic PDT for early-stage central type squamous cell carcinoma in 1980 for the first time in the world, and a complete cure was obtained. Since then, PDT has attracted much attention.

Photosensitizers and lasers with specific wavelengths are the critical points of PDT. Photofrin, sodium porfimer (Japan Lederle Co. Ltd., Tokyo, Japan), and excimer dye laser (Hamamatsu Photonics Co. Ltd., Hamamatsu, Japan) were government-approved for clinical use in Japan in 1994, which is equivalent to FDA approval in the United States. This method is now used clinically in Canada for specific indications and also in the Netherlands. This method is only approved for use with caution in esophageal cancer in America. A total of more than 3,000 tumors in various organs have been treated by PDT so far in 32 countries. The organ most frequently treated was the lung, with 808 cases. A phase II clinical study of PDT for early-stage lung, esophageal, gastric, cervical, and bladder cancer cases was conducted at 15 institutions from 1989 to early 1992.[8]

The use of photodynamic therapy (PDT) in ophthalmology

Photodynamic therapy (PDT), which was first used in ophthalmology in 2000, is a therapeutic procedure that uses a photosensitive intravenous drug, verteporfin, combined with a low-power infrared laser with a long duration. This method is used to treat blood vessel problems in the retina and choroid in the eye. It was first indicated for neovascular age-related macular degeneration (AMD) in a randomized controlled trial showing improved visual acuity compared to a placebo. The role of photodynamic therapy in ophthalmology is driven by the successful treatment of AMD with PDT and verteporfin in the PDT study. Studies have demonstrated the efficacy of PDT in treating AMD patients with classic subfoveal choroidal neovascularization. As new therapies have developed, they are now commonly used as second-line treatment for neovascular AMD. PDT is now most commonly used to treat central serous retinopathy (CSR) cases and is effective by several published studies.[9]

Basic principles of photodynamic therapy (PDT)

The basic principles of PDT are relatively easy to understand. A light-absorbing dye is applied or

injected into the patient, and after a suitable time for maximum absorption into the tumor/target area, the affected area is irradiated with light. The dye absorbs the incident light and is formed electronically. This then produces reactive oxygen species (ROS), which destroy the tumor. The concept is simple, and because the dye is non-toxic in the absence of light, it does not carry the adverse effects of traditional chemotherapy. In PDT, only areas of body tissue are irradiated, which will produce activity that causes cellular damage. As mentioned, there are three components to PDT; light, oxygen, and a photosensitizer. The description of oxygen and photosensitizer is described in the following section.[2]

Oxygen

The result of dye irradiation is the formation of reactive oxygen species, and it is generally considered that singlet oxygen $1O_2$ is the ROS responsible for cell destruction in PDT. $1O_2$ is formed when oxygen, which appears as a triplet ($3O_2$), absorbs energy in its ground state. It is energetically unstable because there are vacant orbitals of the same energy available for the paired electron. Therefore, $1O_2$ is energetically higher (thus more reactive) and will return to its triplet ground state. The lifetime of the singlet state in cells is of the order of 100s ns, and it has been estimated that it can diffuse at less than 50 nm at this time. Therefore, the action is limited to the cellular dimension in micron cells.[10]

O_2 is formed by the transfer of energy from the excited dye. However, there is a possible alternative. Superoxide anion is formed if the excited dye transfers electrons to molecular oxygen. Therefore, the ROS formed is an essential aspect of drug development in PDT. The transfer of electrons to form superoxide anions is called a type I reaction. The transfer of energy that forms 1O2 is called a Type II reaction. We can tell this apart by understanding the chemistry behind it. Type II is detected because when singlet oxygen returns to its triplet ground state, it emits a small amount of infrared phosphorescence, which can be detected (maximum emission around 1270 nm). On the other hand, type I can be detected by monitoring the redox chemistry of Fe^{3+} and subsequent hydroxyl radical formation (a photo-Fenton mechanism).[10]

Photosensitizer

The photosensitizer has several functions and must be located within the tumor. The photosensitizer must also absorb light in the visible region (600 - 800 nm and preferably 700 - 800 nm). Hemoglobin is an essential component of body tissues and strongly absorbs in the central, visible light region (580 nm). This is clear when we shine light through our hands; only red light passes. Therefore, the ideal photosensitizer will absorb light where the body cannot absorb light so that it can be used on deep body tissues (e.g., liver, pancreas).[9,10]

Clinically approved PDT drugs have not been optimized for absorption of more considerable wavelength light, and hence current PDT treatment is limited to areas easily exposed to light sources such as skin, lungs, and esophagus. This problem of depth of penetration was the subject of a recent court case in which a doctor claimed that PDT treatment would not be suitable for treatments such as liver cancer because the liver is too large for light to pass through. Penetration is doubled when the light at a wavelength longer than the absorption of hemoglobin is reached (630 nm) and doubles again at 700 nm. Therefore, an ideal photosensitizer will absorb between 700 - 800 nm. Other factors for an ideal photosensitizer include low toxicity in the absence of light and minimal post-treatment side effects. One of the most significant side effects is post-treatment light sensitivity, in which patients must avoid light due to concerns that healthy body tissue that still contains residual photosensitizers will produce unwanted activity.[7]

The first photosensitizer used clinically for cancer therapy was a water-soluble mixture of porphyrins called hematoporphyrin derivatives (HPD), a pure form known as photofrin. Although photofrin is still the most widely used photosensitizer, it has several disadvantages,

including long-lasting skin photosensitivity and relatively low absorbance at 630nm. While a photodynamic effect can be produced with photofrin, red diversion will enhance efficacy. Red absorbance band and increases absorbance at longer wavelengths. There has been a tremendous effort among medicinal chemists to find a second-generation photosensitizer, and several hundred compounds have been proposed as potential agents for anti-cancer PDT. Table 1 lists the most promising photosensitizers that have been used clinically for cancer PDT (whether approved or in trials).[1]

Table 1. Clinically applied photosensitizer

Clinically applied photosensitizers.

Photosensitizer	Structure	Wavelength (nm)	Approved	Trials	Cancer types
Photofrin (HPD)	porphyrin	630	World wide		lung, esophagus, bile duct, bladder, brain, ovarian
ALA	porphyrin precursor	635	World wide		skin, bladder, brain, esophagus
ALA esters	porphyrin precursor	635	Europe		skin, bladder
Foscan (mTHPC)	Chlorine	652	Europe	US	head and neck, lung, brain, skin, bile duct
Verteporfin	Chlorine	690	World wide (AMD)	UK	ophthalmic, pancreatic, skin
HPPH	chlorin	665		US	head and neck, esophagus, lung
Purlytin (SnEt2)	chlorin	660		US	skin, breast
Taloporfin, LS11, MACE, Npe6	chlorin	660		US	liver, colon, brain
Fotolon (PVP-Ce6), Radachlorin, Photodithazine	chlorin	660		Belarus, Russia	nasopharyngeal, sarcoma, brain
Silicon phthalocyanine (PC4)	phthalocyanine	675		US	cutaneous T cell lymphoma
Padoporfin (TOOKAD)	bacteriochlorin	762		US	prostate
Motexafin lutetium (LuTex)	texaphyrin	732		US	breast

Light source

Blue light penetrates less efficiently through tissue, while red and infrared radiation penetrates deeply. The area between 600 and 1200 nm is often called the optical window of the network. However, only light up to 800 nm can produce O_2 because the longer wavelengths do not have sufficient energy to initiate photodynamic reactions. No single light source is ideal for all indications of PDT, even with the same photosensitizer. Therefore, the choice of the light source should be based on photosensitizer absorption (excitation fluorescence and action spectra), disease (location, lesion size, accessibility, and tissue characteristics), cost, and size. The clinical efficacy of PDT depends on complex dosimetry, i.e., total light dose, time of light exposure, and mode of light delivery (single vs fractionated or even metronomic). Integrated systems that measure the light distribution and degree of smoothness, either interstitial or on the surface of the tissue being treated, have so far only been used in experimental studies.[2,10]

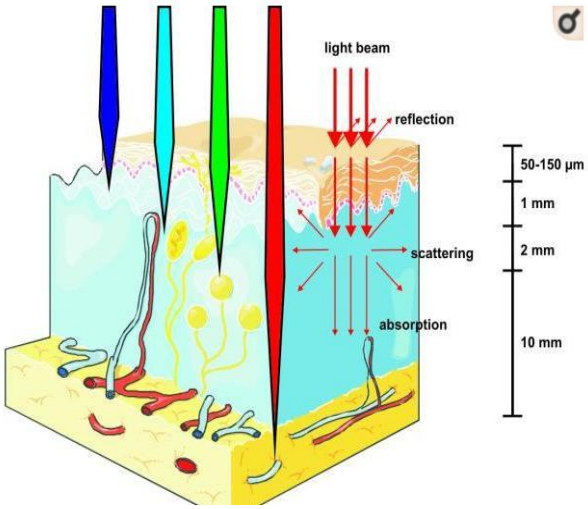

Figure 2. Light propagation in photodynamic therapy

Most photosensitizers in the ground state (i.e., Singlet) have two electrons with opposite spins located in the most energetically favorable molecular orbital. The absorption of light causes the transfer of one electron to a higher energy orbital. These photosensitizers are highly unstable and emit excess energy as fluorescence and heat. In addition, the excited photosensitizer can undergo intersystem crossing to form a more stable triplet state with the reverse spin of one electron. The photosensitizer in the triplet state can either be irradiated to a ground state or transfer its energy to molecular oxygen (O2), which is unique in being a triplet in its ground state. This step leads to singlet oxygen (1O2) formation, and this reaction is referred to as the type II process. Type I processes can also occur where photosensitization reacts directly with organic molecules in the microcellular environment, gaining hydrogen atoms or electrons to form radicals. Subsequent autoxidation of the excited photosensitizer generates superoxide anion radicals (O2 • -). One-electron dismutation or reduction of O2 • - produces hydrogen peroxide (H2O2), which in turn can undergo one-electron reduction to become a strong oxidant, namely the potent hydroxyl radical (HO•). The generation of ROS via type II chemistry is much simpler than via type I, and most photosensitizers are believed to act via type II rather than type I mechanisms.[6,7]

2. Conclusion

Understanding the anatomy of the eye and the basic principles of photosensitizers will increase the effectiveness of this therapy. The photosensitizer absorbs light in the visible region (600 - 800 nm and preferably 700 - 800 nm). The ideal photosensitizer will absorb light where the body cannot absorb light, which can be used on deep body tissues.

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