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Major review

Clinical use of photodynamic therapy in ocular tumors

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ABSTRACT

Although the introduction of intravitreal anti–vascular endothelial growth factor drugs reduced the indications for photodynamic therapy in ophthalmology, it may still be used in various ocular tumors. Although many studies have shown that photodynamic therapy is effective in ocular tumors, the literature consists of case reports and series. In this review, we systematically performed a meta-analysis for the use of photodynamic therapy in circumscribed choroidal hemangioma, diffuse choroidal hemangioma, retinal capillary hemangioma, von Hippel-Lindau angiomatosis, choroidal melanoma, retinal astrocytoma, retinoblastoma, eyelid tumors, conjunctival tumors, and choroidal metastasis.

1. Introduction

1.1. *Photodynamic therapy*

Photodynamic therapy (PDT) is recognized as a minimally invasive and relatively non-toxic treatment modality in which a light-sensitive compound is administered. This compound accumulates in the target tissue and, on illumination, is activated and exerts its effects by triggering the production of reactive oxygen species in the tissue microenvironment.

2. Photosensitizers in medicine

The light-sensitive compounds used in PDT are called photosensitizers. Although a wide variety of light-sensitive compounds are used in other branches of medicine, the most common light-sensitive compound in ophthalmology is verteporfin. In clinical use, photosensitizers are divided into porphyrinoids, chlorins, and dyes.[8] (Table 1) Photosensitizers were previously classified as first-, second- and third-

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Table 1 – Photosensitizers

Photosensitizer	Indications
Porphyrins	
Levulan (aminolevulinic acid)	Approved by FDA for actinic keratosis
Metvix (methyl aminolevulinate)	Approved by FDA for actinic keratosis
PHOTOFRIN (porfimer sodium)	Approved by FDA for esophageal cancer and lung cancer
Foscan (temoporfin)	Approved by EU for squamous cell carcinoma and early lung cancers, no FDA approval
Laserphyrin (talaporfin)	Approved in Japan for photodynamic therapy of early-stage lung cancer
Visudyne (verteporfin)	Approved by FDA for subfoveal, predominantly classic, choroidal neovascularization
Purlytin (rostaporfin)	FDA granted fast-track status to rostaporfin for treatment of age-related macular degeneration[5]
TOOKAD (WST-11)	Under clinical trials; prostate cancer
Chlorins	
Foscan (temoporfin)	Approved by EU for squamous cell carcinoma and early lung cancers, no FDA approval
Photochlor (HPPH)	Under clinical trials
Photolon	Under clinical trials; cervical intraepithelial neoplasia
Photoditazin	Under clinical trials; pulmonary neoplasm
Radachlorin (sodium-chlorin e_6,p_6)	Under clinical trials; oral cancers
Dyes	
IC-Green (indocyanine green)	Approved by FDA for determining cardiac output, hepatic function and liver blood flow, and for ophthalmic angiography
Photosens (phthalocyanine)	Under clinical trials; superficial bladder cancer
Phenotiazinium (methylene + toluidine blue)	Under clinical trials
Naphthalocyanine	Under animal trials

EU, European Union; FDA, Food and Drug Adiministration; HPPH, 2-(1-Hexyloxyethyl)-2-devinyl pyropheophorbide-a.

generation photosensitizers. First-generation photosensitizers, mainly porphyrins, were developed in the 1970s and early 1980s. Derivatives of porphyrins, such as biologic conjugates, which are modified porphyrins, are second-generation photosensitizers developed in the 1980s.[86] Dividing photosensitizers into generations, however, is no longer universally accepted, and improvement across generations is not justified.[8] Porphyrins intensely absorb light at approximately 410 nm, whereas chlorins strongly absorb light in the red spectrum, that is, between 640 and 700 nm.

Photosensitizers are used in medicine for photodynamic diagnosis and PDT. They tend to accumulate in tumors more than in normal tissues, primarily because of the increased nuclear-cytoplasmic ratio and the higher anabolic processes.[181] Another factor is the higher permeability of tumor microvasculature, which causes photosensitizers to extravasate into surrounding tissues.[149] Although the amount of the photosensitizer in circulation is temporarily high in agents such as aminolevulinic acid or benzoporphyrin derivative monoacid ring A, sun avoidance is adequate. In longer-acting agents such as PHOTOFRIN, some patients may remain photosensitive for up to 90 days; therefore, sun avoidance alone is problematic and specially designed highly protective fabrics such as Solumbra (Sun Precautions) may be needed. After verteporfin treatment, patients are advised to avoid direct sunlight and bright halogen lights for 5 days.

Indocyanine green (ICG), a dye-type photosensitizer, is particularly interesting because it is widely used in medical diagnostics, especially in ophthalmology and in PDT, to selectively overheat cancer cells. ICG is also used in plastic surgery for the investigation of skin and muscle transplant circulation, in abdominal surgery for gastrointestinal anastomosis, in general surgery for wound healing and ulcers, in internal medicine for diabetic extremities, in heart surgery in aortocoronary bypass, and in periodontal therapy for its antimicrobial effects. ICG absorbs near-infrared radiation, and if illuminated with light, especially at a wavelength of approximately 805 nm, ICG releases heat and free radicals, such as singlet oxygen, that damage target cells. ICG is also used in ocular PDT.

3. Light delivery

Noncoherent light sources, light-emitting diodes, and lasers are used for PDT.[25,180] Noncoherent light sources and conventional arc lamps are often preferred because they are less expensive, produce a wide spectrum of light, and may be used with various photosensitizers. In conjunction with filters, they may also be used for output-selective wavelengths. The LumaCare is a compact portable fiber-optic delivery system[163] that produces light between 350 and 800 nm with interchangeable probes and optical filters. Noncoherent light sources, however, have the disadvantages of significant thermal effect and low light intensity.

Light-emitting diode applicators can be produced in different sizes to fit into a balloon catheter for brain tumors[168] or into a tumor percutaneously for minimally invasive interstitial PDT.[33,111] Laser systems can be easily focused into fiber delivery systems and moved into otherwise inaccessible locations such as the urinary tract or the brain. Thus, the type of illumination differs according to the localization of the lesion: bronchoscopic for pulmonary diseases, endoscopic for gastroenterology, transurethral for urologic diseases, and intraoperative cavitary illumination for brain tumors.[86]

Every photosensitizer has its own absorption spectrum. The penetration depth of a light source is increased with the wavelengths in the visible and the near-infrared spectral regions.[82] The main sensitizers used for PDT to date have been complex mixtures of porphyrins, which absorb light poorly in the red region of the spectrum (>600 nm). Therefore, there is interest in creating a photosensitizer that absorbs light