Medical progress

Photodynamic therapy for malignant and non-malignant diseases: clinical investigation and application

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Photodynamic therapy (PDT) is a relatively new treatment modality. Clinical PDT procedure involves the administration of a photosensitizer followed by local illumination with visible light of a specific wavelength. In the presence of molecule oxygen, the light illumination of photosensitizer can lead to a series of photochemical reactions and consequently generate a variety of cytotoxic species. The nature, location and quantity of PDT-induced cytotoxic species and the sensitivity of the target cells determine the outcome of a PDT treatment. Since the first government approval of photosensitizer Photofrin was granted, for the treatment of bladder cancer in Canada in 1993,[1] the utilization of PDT in the treatment of malignant and non-malignant diseases has increased significantly due to the improvement in photosensitizers and light applicators. Several similar photosensitizers have been developed and utilization in China since the 1980s.[2]

Photosensitizer is a critical element in PDT. Major side-effects associated with the first generation photosentizer [e.g. Photofrin (porfimer sodium) Axcan Pharma; Birmingham, AL, USA], such as prolonged skin photosentitization, have been improved in the second generation photosensitizer (e.g. Visudyne; Novartis Pharmaceuticals Corporation; East Hanover, NJ, USA). Several first and second generation photosensitizers have received national or regional regulatory approval and some promising ones are currently under clinical trials (Table 1).

Conventional lamps, light emitting diode (LED) and lasers have been used as non-thermal light sources in PDT procedures. The KTP-dye modular (Laserscope PDT Dye Module) was the most widely used PDT laser prior to the approval of the portable, lightweight and less expensive diode lasers (e.g. DIOMED 630 PDT; Diomed, Inc.; Andover, MA, USA). Lasers have many advantages. Their monochromaticity improves effectiveness if the wavelength of the laser corresponds with the peak absorption of photosensitizer. Lasers can produce high irradiance to shorten the treatment time. Lasers can be readily coupled to optic fibers and enable light to be delivered to any organ. However, in the treatment of large skin lesions, noncoherent light sources are superior to laser systems because of their large irradiation field. In some PDT procedures, balloon catheters and light diffusing media have been used in conjunction with laser and optic fiber to provide uniform light distribution and better positioning. The choice of a specific light delivery mode in clinical settings can be based on the nature and location of the disease (Table 2).

The modern PDT in oncology dates back to the early 1970s, when Thomas J Dougherty (Roswell Park Cancer Institute, USA), re-discovered hematoporphyrin derivative (HpD) and began investigating the mechanisms and clinical applications of antitumor PDT.[1] PDT started in China in the early 1980s shortly after domestically produced HpD became available.[3,4] A recent literature survey of Chinese BioMedical Citation Database (CBMdisc) studied more than 60 Chinese journal articles published between

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Table 1. Regulatory status of some common PDT photosensitizers

Photosensitizer	Abbreviation	Generic name	Manufacturer
Approved			
Polyhematoporphyrin ether/ester	Porfimer sodium	Photofrin	Axcan Pharma, Inc.
Hematoporphyrin derivatives	HpD	Photogem	Moscow Institute of High Chemical Technologies
Hematoporphyrin derivatives	HpD	Photosan	SeeLab F&E GmbH
Hematoporphyrin derivatives	HiPorfin	Hematoporphyrin Injection	Chongqing Huading Modern Biopharmaceutics Co. Ltd.
Benzoporphyrin derivative monoacid ring A	BPD-MA, verteporfin	Visudyne	Novartis Pharmaceuticals
5-aminolevulinic acid	ALA	Levulan	DUSA Pharmaceuticals, Inc.
Methyl aminolevulinate	MLA	Metvix	PhotoCure ASA
Meta-tetrahydroxyphenylchlorin	mTHPC, temoporfin	Foscan	Biolitec AG
Mono-L-aspartyl chlorin e6 or talaporfin sodium*	NPe6, ME2906	Laserphyrin	Meiji Seika Kaisha, Ltd.
Sulfonated aluminum phthalocyanine	$AlPcS_{2-4}$	Photosens	General Physics Institute
Tolonium chloride or Toluidine Blue O	TBO	SaveDent PAD	Denfotex Ltd.
Currently under clinical trial			
Lutetium(III) texaphyrin or motexafin lutetium	Lutex	Antrin	Pharmacyclics Inc.
Tin ethyl etiopurpurin	SnET2, purlytin	Photrex	Miravant Medical Technologies
Hematoporphyrin monomethyl ether	HMME	Hemporfin	Fudanzhangjiang BioPharmaceutical Co., Ltd.
deuteroporphyrins	DpD	Duetpofin	Fudanzhangjiang BioPharmaceutical Co., Ltd.
2-[1-Hexyloxyethyl]-2-devinyl pyropheophorbide-a	HPPH	Photochlor	Roswell Park Cancer Institute
Pd-bacteriopheophorbide	WST09	Tookad	Negma-Lerads and Steba Laboratories Ltd.

*Under clinical trials have different names: LS11 or Litx; PDT: photodynamic therapy.

Table 2. Common light delivery modes

Light delivery modes	Description	Example
Front superficial irradiation	A uniform irradiance incident beam delivered to a front surface by a microlens fiber externally.	Skin PDT
Cavity superficial irradiation	An isotropic source centered in a spherical cavity and delivering light to the cavity surface.	Brain tumor PDT
Cylindrical superficial irradiation	A cylindrical diffuser source centered in a cylindrical lumen.	Esophageal PDT
Cylindrical interstitial irradiation	A cylindrical diffuser source embedded in the target tissue.	Solid tumor PDT

1990－2001 and concluded that near 4000 cancer patients had undergone PDT treatment in mainland China.[5] Much progress has been seen in basic and clinical investigation and clinical application worldwide in recent years.[6,7] This manuscript will review the clinical data published in China and abroad, and summarize the recent progress in clinical applications and investigational studies. Some of the important progress in PDT clinical applications for the management of both malignant and non-malignant diseases will be discussed.

PDT for treating malignant diseases

Skin premalignant and malignant diseases

The feasibility of PDT for skin diseases were studied due to the easy accessibility of the skin to the topical application of photosensitizer and light. Because of good cosmetic outcome, PDT is particularly suitable for lesions in the face and neck area. In the 1970s, HpD and xenon arc lamp have been used to treat skin cancers. Early studies demonstrated that the primary skin cancers that showed a 20%－80% complete response (CR) included squamous cell carcinomas (SCCs), basal cell carcinomas (BCCs) and malignant melanomas, and the secondary cancers originating from breast cancer, colon cancer and endometrium cancer.[8,9] Similar procedures have been used in China with their data indicating that multi-session treatment can achieve a higher CR (－90%) for BCCs and SCCs.[10,11]

Since the discovery of endogenous protoporphyrin IX (PpIX) photosensitization induced by exogenous administration of prodrug 5-aminolevulinic acid

(ALA), premalignant and malignant skin lesions have become a target of ALA-PDT. Early multi-center clinical studies of actinic keratosis (AK) showed that ALA-PDT (Levulan and Blu-U blue light system) resulted in a high CR and disease-free rate. AK became the first approved dermatologic indication of ALA-PDT in USA in 2000. Recently, methyl aminolevulinate (Metvix) has also been approved for AK in Australia, Europe and USA. Domestically produced ALA is currently undergoing similar trials in China.

Clinical investigations of ALA-PDT have been extended to BCCs, SCCs, SCC *in situ* (Bowen's disease), cutaneous T-cell lymphoma, basaloid follicular hamartomas, extramammary Paget disease, and sebaceous gland hyperplasia in China and other countries in recent years.[12-21] PDT may also be useful for both Mediterranean and HIV-related Kaposi's sarcomas since it can be repeated and will not cause significant immunosuppression.[22] Recent clinical data also suggests that PDT might be useful for the treatment of the pigmented malignant melanomas although in general PDT is considered unsuitable for the pigmented lesion due to a limited light penetration.[23]

Ophthalmic tumor

Several case studies demonstrated that Verteporfin-PDT could resolve the exudative retinal detachment associated with a diffuse choroidal haemangioma. An investigational study of circumscribed choroidal haemangioma showed evidence of tumor flattening, reducing subretinal fluid and choroidal vasculature.[24]

Head and neck cancer

Photodynamic therapy is particularly suitable for the treatment of head and neck cancers because it has little effect on underlying functional structures and has an excellent cosmetic outcome. PDT has been employed in the treatment of malignancies of the oral mucosa, particularly multi-focal squamous cell carcinoma. The treated sites characteristically show erythema and edema, followed by necrosis and frank ulceration. The ulcerated lesions typically take up to eight weeks to heal fully, and supportive analgesia is required in the first few weeks.[25]

Foscan (Temoporfin; Biolitec Pharma Ltd., Dublin, Ireland) was approved in Europe in 2001 for the palliative treatment of advanced head and neck cancers. Foscan-PDT can have significant clinical benefits and improve the quality of life.[26-28] Several clinical trials are currently under way to evaluate the efficacy of other promising photosensitizers, including Photofrin, ALA and Photosens. For patients with advanced disease, the combination of PDT and radiotherapy or surgery could also improve cure rates.

An early Photofrin-PDT study of 107 patients shows that cure for T1 and *in situ* cancer of the vocal cords could be achieved with a single treatment. There was only one recurrence in 25 patients in 79 months of follow-up. All patients responded initially and the cure rate for early oral cavity tumors was 80% after 70 months.[29]

The Chinese pioneered a PDT protocol for nasopharyngeal carcinoma in the 1980s. Zhao et al[30] reported their preliminary HpD-PDT study of 12 patients in 1987. Eight patients (7 $T_1N_0M_0$, 1 $T_1N_2M_0$) were newly diagnosed and four had failed in radiotherapy. Histopathologic examination confirmed that 11 were low-grade carcinoma and 1high-grade carcinoma. Patients received a total of 2－7 repeat treatments. CR was seen in four patients (33%) including 2 who had failed in radiotherapy and PR in eight patients (67%). No recurrence was reported during 4－16 months of follow-up. Later, Sun et al[31,32] reported treatment results of recurrent nasopharyngeal carcinoma of 191 patients in the 1990s. All patients had failed in radiotherapy: 120 showed recurrence and 71 residual lesions after radiotherapy of maximal dose. Histopathologic examination confirmed that all were high-grade carcinoma at stage $T_1N_0M_0$. The Authors claimed that all patients showed therapeutic response (55.0% CR, 34.6% PR, and 10.5% MR). Various degrees of nasal congestion, nasal discharge, and headache were reported. However, these symptoms were mild and did not need treatment. A five-year follow-up was carried out for 130 patients. Three-year and five-year survival was reported as 44.6% and 25.4%, respectively.

Brain tumor

Cavitary PDT procedure was introduced in the 1990s, which utilizes an optical fiber in a light-diffusing medium, to irradiate the cavity following surgical

resection.[33] Several multi-center studies are currently under way to evaluate the efficacy of Photofrin, ALA, BPD-MA and Foscan.[34-37] A novel photosentitizer HMME-mediated PDT has been studied in 34 glioma patients in China. One- and two-year survival rates were 82% and 53%, respectively.[38] A long-term evaluation of Photofrin-PDT has shown prolongation of survival in patients with malignant gliomas.[39] Optimizing photosensitizer uptake, elevating light dose, combined with interstitial chemotherapy and fluorescence-guided resection might improve the efficacy of intra-operative PDT.[36,37, 40-42]

Pulmonary and pleural mesothelial cancer

Photodynamic therapy has been used to treat bronchogenic carcinoma in China since the 1980s.[43] The worldwide data now show that bronchoscopic PDT is an effective therapy for superficial and early stage non-small cell lung cancer (NSCLC) and serves as a palliative therapy in the treatment of obstructive cancers of the tracheobronchial tree. Bronchoscopic PDT has now achieved the status of a standard protocol for centrally located early-stage lung cancer in Japan. PDT for treating endobronchial metastatic tumors effectively decreased the amount of endobronchial obstruction, and improved quality of life. A new protocol using percutaneous insertion and intra-tumor illumination has been developed for the curative treatment of localized peripheral lung cancer (< 1 cm) unsuitable for surgery or radiotherapy. Preliminary results have shown a partial response in the majority of patients.[44] The same Japanese group also studied the efficacy and mechanisms of NPe6-PDT for SCCs. A recent Chinese study of 23 patients demonstrated that Photosan-PDT also showed high efficacy for treatment of primary or recurrent bronchial lung cancer.[45]

Malignant pleural mesothelioma, often related to asbestos exposure, responds poorly to conventional therapies. Photofrin-PDT has been tested as an adjuvant intra-operative modality in several countries. The preliminary data demonstrate the safety and feasibility of intrapleural PDT which offers good survival results for stage I or II patients. However, for stage III or IV patients, PDT could not significantly prolong survival or improve local control. In recent years the improvement in photosensitizers and PDT techniques has led to a renewed interest in intrapleural PDT.[46] Hyperoxygenation is an effective method to enhance PDT-induced cytotoxicity.[47] Therefore, it is expected that carrying out the intrapleural PDT under hyperoxygenation conditions might further enhance PDT efficacy.[48]

Breast cancer

Locally recurrent breast carcinoma on the chest wall occurs in 5%－20% of breast cancer patients. Several reports suggest that Photofrin-PDT or Foscan-PDT can offer 14%－73% CR and 14%－45% PR, but the duration of response is variable (6 weeks － 8 months).[49,50] It is expected that the photosensitizer acting at longer wavelengths can achieve deeper tissue penetration thereby greatly expanding the patient population for which this modality will become more useful.

Gastroenterological cancer

Endoscopically accessible premalignant or malignant lesions located in the esophagus, the stomach, the bile duct or the colorectum with a high surgical risk are favorable targets of endoscopic PDT. Photofrin-PDT has now been approved for treating obstructive esophageal cancer, early-stage esophageal cancer and Barrett's esophagus in several countries. A longer diffuser tip and the light centering balloon (e.g. Xcell PDT Balloon; Wilson-Cook Medical Inc.; Winston-Salem, NC, USA) are able to treat a large area of esophageal mucosa during a single treatment. It is suggested that optimizing light dose and re-treating small areas of residual or untreated Barrett's mucosa may reduce the post-PDT stricture formation and improve the overall efficacy.[51] Endoscopical GI PDT has been explored in China since the early 1980s.[52,53] In recent years more experience and improved outcomes have been obtained using domestic or imported HpD products.[54-57]

Cholangiocarcinoma is a rare tumor that continues to present formidable challenges in diagnosis and treatment. In recent clinical investigations of a small number of patients (n=20) with unresectable cholangiocarcinoma and failed in endoscopic stents, PDT induced a decrease in bilirubin levels, improved quality of life for an extended period, and led to a slightly better survival.[58] Endoscopic guided illumination of the biliary tract is safe and effective for

inoperable hilar cholangiocarcinoma. However, these studies are not randomized, and further investigation is needed in order to determine if PDT is a useful adjuvant tool for cholangiocarcinoma.

Due to advances in light applicators, the interstitial PDT is now becoming a practical option for solid tumors, including those in parenchymal organs such as the pancreas and the liver. The first pilot study of Foscan-PDT on inoperable pancreatic cancer was carried out in the UK. The percutaneous interstitial protocol, of multiple diffuser fiber illumination, could produce significant necrosis and prolong survival time. In most cases, the necrotic area of the treated tumor healed safely. There was no sign of a pseudocyst, abscess, or pancreatic duct leak. These promising results encourage larger scale trials to further assess the feasibility of pancreas PDT.[59]

A pilot study of ultrasound guided percutaneous interstitial PDT for the treatment of advanced liver cancer has been reported by Chinese clinicians in the 1990s.[60,61] This study included 63 hepatocellular carcinomas, 2 cholangiocarcinoma, 1 hepatoblastoma, 1 tubular adenocarcinoma and 3 poorly differentiated adenocarcinoma. Fifty-six patients were newly diagnosed and the other fourteen had either failed in chemotherapy or post-resection recurrence. Thirty-three patients had local or distance metastasis during the treatment. Tumor sizes ranged from 5 cm to >15 cm. Thirty patients received one-session treatment and forty multi-session treatments. At one month post-PDT the sonographic scan showed a slight signal enhancement in treated areas and tumor boundaries remained visible and the size became smaller. CT scans confirmed tumor necrosis and the reduction of tumor mass. The histopathologic examination indicated a mix of necrosis, inflammation and fibrosis in the treated areas. No damage was detected in the surrounding normal tissue. One patient underwent resection one month post PDT. Histopathologic examination showed larger areas of tumor necrosis. The preliminary results of this study suggested that PDT was effective and safe for the treatment of inoperable large primary and recurrent liver cancers. Multiple treatments can enhance both short-term and long-term survival.

Urological cancer

The feasibility and efficacy of PDT for the treatment of primary and recurrent bladder cancer were first to be studied using domestic HpD products and various laser systems in China since the early 1980s.[62-66] Photofrin obtained its first Canadian regulatory approval for recurrent papillary tumors in 1993. Intravenous Photofrin administration followed by intravesical illumination became an option for patients with refractory tumors. The initial response to a single treatment of the whole bladder tends to be good, but side effects such as bladder contraction and irritation are noticeable and the incidence of relapse within a year is high.[67-69] Since the side effects are dose dependent, fractionating drug and light doses in a sequential PDT mode might subside cancerous cells and meanwhile reduce local toxicity.[70] Bladder cancer tends to be a superficial condition, a superficial treatment mediated with ALA or its ester derivatives may be better. Nonetheless, intravesical instillation of ALA can eliminate cutaneous phototoxicity. Several clinical investigations show that ALA-PDT is an effective treatment option for patients with superficial bladder cancer who have failed in transurethral resection and/or intravesical BCG immunotherapy.[71,72] It has been shown that by repeating PDT treatments, it is possible to further inhibit the progression of bladder cancer.[73]

Prostate cancer is still a significant health problem in the Western world. Recent clinical trials of Foscan-PDT and ALA-PDA on patients who had failed in radiotherapy showed a post-PDT decrease in prostate specific antigen (PSA) levels.[74,75] The preliminary results from two ongoing clinical trials of motexafin lutetium-PDT and Tookad-PDT designed to totally ablate the entire prostate gland are also encouraging.[76-78] The total ablation approach involves the implantation of multiple diffuser fibers into the prostate gland through a transperineal brachytherapy template. It should be fully recognized that characterization of light penetration and distribution in prostate is important due to the significant inter- and intra-prostatic differences in the tissue optical properties. Several recent studies suggest that a real-time drug/light dosimetry measurement and feedback system for monitoring drug concentrations and light fluences during interstitial PDT should be considered.[79] Protection of the pelvic nerve also becomes an inevitable challenge during total ablation.[80]

Gynecological cancer

Prior to and after its regulatory approval in Japan in 1994, Photofrin has been used successfully to treat carcinomas *in situ* and dysplasia of the uterine cervix. Several Japanese studies have shown that colposcopic-assisted cervical canal illumination after intravenous Photofrin administration can achieve a high CR (< 94%) and preserve fertility.[81] A modified protocol that combined topical administration of Photofrin and superficial illumination demonstrated that CR was light dose dependent for cervical intraepithelial neoplasia (CIN). Several *in vivo* studies have demonstrated selective absorption of ALA by dysplastic cervical cells. This led to the presumption that ALA therefore represents a promising photosensitizing prodrug for the treatment of CIN with ALA-PDT.[82] However, several randomized, double-blind, placebo-controlled clinical trials showed that ALA-PDT was well tolerated by patients but the general consensus is that ALA-PDT has a minimal effect in the treatment of CIN 2 and CIN 3.[83]

A recent pilot study of topical application of ALA and superficial illumination for the treatment of vulvar and vaginal intraepithelial neoplasia (VIN, VAIN) shows that ALA-PDT is as effective as conventional treatments though not equally efficacious for all subgroups, but with shorter healing time and excellent cosmetic results.[84]

Photodynamic therapy has also been employed to treat ovarian cancer and both benign and malignant lesions of the endometrium. But no reliable clinical results have yet been shown in limited clinical trials.

PDT for treating non-malignant diseases

Dermatological disease

The importance of antibiotic resistance in dermatological practice is increasing. An alternative approach may be to use PDT. One of the advantages of the broad spectra of antimicrobial PDT is the development of resistance to photodynamically induced direct killing which would be unlikely.[85,86]

A number of other clinical conditions, such as acne vulgaris, psoriasis, viral warts and hair removal, are currently under clinical investigation. Several Chinese groups also studied the feasibility of ALA-PDT for the treatment of anogenital condylomata acuminate. Initial results showed a high CR rate and a low recurrence rate.[87,88]

Another potential application is the treatment of port-wine stain (PWS), a capillary vascular malformation, with vascular targeted PDT to induce selective injury of only the abnormal blood vessels in the dermis while sparing the normal overlying epidermis although PWS PDT studies outside China are still limited and the clinical outcomes are still controversial.[89] However, several Chinese studies demonstrated that PDT was an effective and safe modality for treating PWS.[90-95] In a retrospective survey of single hospital clinical data, [96] Gu et al[90,91] reexamined a large number of patients (1216 patients with 1632 lesions; 10 months to 65 years old) who underwent HMME-PDT (774 lesions) or HpD-PDT (858 lesions) during April 1991 and January 2000. They described PWS as a pink (*n*=158), purple (*n*=1070), thicker or nodular lesion (*n*=404). In their pilot study, HMME or HpD was given at dosages of 3.0－7.0 mg/kg and the area of light irradiation was 3－127 cm^2. Light fluences of 90－540 J/cm^2 were delivered at 50－100 mW/cm^2 by argon ion laser (488.0 and 514.5 nm) or copper vapor laser (510.1 and 578.2 nm). Therapeutic responses were examined visually and recorded in five Grades: I - excellent (complete blanching, become normal skin), II - good (marked blanching, thicker lesion become flat), III - fair (significant blanching, thicker lesion become flat moderately), IV - poor (slight blanching, thicker lesion become flat slightly) and V - no change (no change). All lesions showed responses to a single or multiple treatments. Fair (III)-to-excellent (I) responses were seen in 94.8% of the lesions in HMME group and 93.7% in HpD group. No recurrent was reported during 2 months to 9 years of follow-up of 58% patients. They concluded that both HMME-PDT and HpD-PDT were effective but the former had advantages of fewer acute reactions, faster healing and short skin photosensitization. This group also conducted blood perfusion study in 28 lesions of 24 patients and showed that a marked decrease in blood perfusion was seen after PDT in all lesions and the difference between before and after PDT was statistically significant even at six months after PDT.[97] Localized post-PDT treatment responses such as edema, scarring and hyperpigmentation were

reported. Those responses were temporary and the authors claimed that thicker scars usually peeled off within 6－8 weeks after PDT.[91] Other hospitals reported that in their trial of 80 subjects (2.5－65.0 years old) all subjects experienced a various degree of HMME-PDT related pain and younger subjects (under age 14) required a general anesthesia.[93]

Ophthalmic disease

Liposome-encapsulated BPD-MA (benzoporphyrin derivative monoacid ring A) under the generic name of Verteporfin or Visudyne® was synthesized in the mid 1980s with an intention for cancer treatment. However, it has been used primarily for ocular PDT. Several well designed clinical studies in North America and Europe showed that age-related macular degeneration (AMD) treated with Verteporfin were more likely to experience stabilized vision than a control group.[98] Therefore, Verteporfin-PDT, approved for AMD worldwide since 2000, should be considered as a first-line therapy in these difficult-to-manage conditions such as subfoveal choroidal neovascularisation (CNV) secondary to AMD, pathological myopia or presumed ocular histoplasmosis syndrome. China adopted Verteporfin-PDT in 2000 and has successfully treated more than 100 eyes including classic CNV, exudative AMD, central exudative chorioretinititis and high myopia.[99-102] Several clinical trials are currently under way to evaluate the efficacy of ocular PDT of other promising photosensitizers including tin ethyl etiopurpurin, motexafin lutetium and mono-L-aspartyl chlorin e6.

Dental disease

Technical challenges of conventional therapeutic procedures extend from the continued struggle against two of the most common infectious diseases -dental caries and periodontal diseases-to eliminating life-threatening oral and pharyngeal malignancies and other conditions that compromise oral health and the quality of life. Implementation of PDT for the treatment of oral infection and malignancy face similar or even greater challenges due to the need of delivering sufficient photosensitizer and light to a complex structure.

It has been shown that phenothiazinium dyes mediated PDT is effective in killing bacteria in complex biofilms, such as subgingival plaque, which are typically resistant to the action of antibiotics.[103] Systems using tolonium chloride (toluidine Blue O, TBO) and low power 635 nm laser for the treatment of endodontics and caries are now available commercially under the trademark of PAD (Photo-Activated Disinfection; Denfotex Ltd., Fife, UK). Since 635 nm laser light transmits well across dentine, locally applied TBO can be used effectively in carious lesions. In dental caries the use of PAD can eliminate residual bacteria in softened dentine and provide an environment which encourages rapid healing. This means that less tissue is removed and thus cavity repair is more conservative. In addition, endodontic PAD might lead to accelerated post-operative bone regrowth. Other possible clinical applications include disinfection of root canals, periodontal pockets, deep carious lesions and sites of peri-implantitis, and prevention of alveolar ostitis and post-extraction pain.

Cardiovascular disease

Preclinical studies show motexafin lutetium could be taken up by atherosclerotic plaque and concentrated within macrophages and vascular smooth muscle cells. This leads to several phase I trials in US and Japan to develop endovascular photoangioplastic modality for cardiovascular diseases such as intimal hyperplasia, and atherosclerosis or vulnerable plaque, and prevention of restenosis after coronary-stent placement. Preliminary results suggest that PDT might be useful for the treatment of flow-limiting coronary atherosclerosis or vulnerable plaque while sparing normal surrounding vascular tissues.[104,105] Several recent Chinese studies using various animal models also suggest that PDT may be beneficial in reducing intimal hyperplasia.[106,107]

Urological disease

Benign prostatic hyperplasia (BPH) is a common condition of aging men. There has been a renewed interest in transurethral PDT in recent years and there is an ongoing Phase I/II dose escalation study to assess the feasibility of transurethral PDT for the management of BPH with lemuteporfin (also known as QLT0074).

Prospects

There is still a strong and increasing interest and research effort internationally focusing on developing new photosensitizers, exploring PDT mechanisms at

molecular and tissue levels, enhancing PDT efficacy with combined modality, and evaluating potential clinical indications. The number of scientific articles on PDT clinical applications as well as basic science steadily increases in both English and Chinese literatures. Review articles on past work, new aspects and future applications have been published on a regular basis while new technology and promising applications continue to be discovered.

Each year several national, regional and international meetings are held regularly which bring together these interests as well as scientists and their research. For example, the World Congress of International Photodynamic Association (IPA), the annual symposium of Biomedical Optics of Photonics West organized by the International Society for Optical Engineering (SPIE), the annual meeting of the European Society for Photodynamic Therapy in Dermatology (Euro-PDT), and the International Symposium on Photodynamic Diagnosis and Therapy in Clinical practice. PDT sessions could also be found in laser medicine, biophotonics and photobiology meetings. The next IPA World Congress will be held in Shanghai China in 2007 (*www.ipa2007-shanghai.com*). This arrangement indicates recognition and appreciation of PDT activities in China by the IPA officials. This conference will offer a good opportunity for Chinese PDT workers to present their work to the international PDT community. A dedicated PDT website (*www.pdt-med.com*) has been established in China. This bilingual website provides up to date techniques, literature and conference information for clinicians, researchers, patients and the general public.

Although regulatory approvals for the clinical use of PDT photosensitizers and light applicators now exist in many countries the total number of approved clinical indications is still limited. There is still a need for involvement from pharmaceutical industries and research institutes to continue to launch clinical trials, to evaluate applications of PDT in conjunction with, or as a replacement for, conventional approaches.

There is little argument that over the past decade PDT has moved beyond the lab bench into the general practice. Some clinical applications such as the treatment of AMD, AK and malignant diseases have entered the mainstream of medical specialties. The anti-tumor efficacy of PDT might be enhanced through an effective immunoadjuvant to further expand its usefulness for a possible control of primary tumor and distant metastases.[108] In the future, it is expected that combined modality and individualized treatment plans will become an essential component of PDT practice over the next decade.

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