INTERNATIONAL JOURNAL OF MULTIDISCIPLINARY ADVANCED RESEARCH TRENDS
ISSN : 2349-7408
VOLUME II, ISSUE IV, MAY 2015

PHOTODYNAMIC THERAPY- A REVIEW

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ABSTRACT

Photodynamic therapy (PDT) is an experimental cancer treatment modality. PDT is based on the accumtilation of a photosensitive dye in premalignant and malignant lesions. A certain period of time after the dye has been administered, tumor tissue may contain more of the sensitizer then the surrounding normal tissues. When tissue containing the sensitizer is exposed to light of a proper wavelength and dose, a photochemical reaction between sensitizer and light will occur. The activated photosensitizer reacts with available oxygen which subsequently damages cells and eventually may cause necrosis of the tumor. Photosensitizers can also be used for fluorescence detection. If a tumor contains more of the photosensitizer than the surrounding normal tissue, its fluorescence can potentially be utilized to detect tumors. This review describes the history, components and mechanisms of PDT with an account of current clinical studies in of the treatment of premalignant and malignant lesions.

Introduction

The concept of tumour localizing drugs which can be activated by visible light to produce selective tumour necrosis has captured the imagination of the clinician, scientist and general public. This concept is referred to as photodynamic therapy (PDT) and is defined as the phenomenon of oxygen-dependant photosensitization. PDT is mainly associated with the treatment of cancer, but is also being applied to premalignant and benign diseases.(1)

History

The use of light in medical therapy has its origins in ancient Greece, Egypt and India. In India, as early as 1400 BC, the plant extract psoralens was used as a photosensitizer for the re-pigmentation of vitiligo. In 1974, the combination of psoralens and ultraviolet A irradiation (PUVA) was found to be effective in the treatment of psoriasis. PUVA therapy is now used for a wide variety of

dermatological diseases such as psoriasis, parapsoriasis, cutaneous T cell lymphoma, atopic eczema, vitiligo and alopecia areata and also used in treatment of premalignant and malignant lesions affecting the oral cavity. (1)

Mechanism of action

The therapeutic effect PDT for the treatment of cancer relies upon tumour localization of the photosensitizer, the concentration and distribution of the photosensitizer within tumour tissue, the oxygen level and light dose absorbed by the photosensitizer (2). There have been a number of hypotheses proposed to explain the selective uptake or retention of porphyrins in tumour cells. These relate to a decreased intratumour pH, carriage by lipoproteins, increased phagocytosis of porphyrin aggregates and a combination of increased leakiness of tumour vasculature and reduced lymphatic drainage (3). The association of haematoporphyrin, haematoporphyrin derivative, porfimer sodium and benzoporphyrin derivative with low-density lipoprotein has been shown to enhance delivery to tumours in mice. However, it has been suggested that tumour-associated macrophages are largely responsible for the higher concentration in tumours. Tumour-associated macrophages may accumulate porphyrins by phagocytosis of aggregates or by the scavenging of modified lipoproteins (4).

Photodynamically induced tissue damage is thought to be the result of the generation of cytotoxic singlet oxygen through a type II photochemical reaction. The initial sites of PDT damage within cells are the cellular membranes, mitochondria and nucleus. Although there is evidence of direct tumour cell killing, the predominant target of PDT is the tumour vasculature. DNA strand breaks have been demonstrated following PDT but PDT has not been shown to be mutagenic in in vitro models (5).

Photosensitizing drugs

The ideal photosensitizer for PDT should be a single pure compound that is non-toxic and should have a short half-life, specific binding to tumour, high quantum yield of singlet oxygen and an activation spectrum between 700 and 800 nm. Photosensitizers of differing properties may be used in combination to produce a synergistic effect (6).

Haemaroporphyrin derivatives

Most experience in PDT has been gained using haematoporphyrin derivatives as photosensitizers. Haematoporphyrin was first made by Scherer from dried blood in 1841. In 1913, Meyer-Betz injected himself with 200 mg of

haematoporphyrin and within minutes of light exposure he developed severe pain and swelling confined to light-exposed areas (7). He remained photosensitive for more than 2 months. In 1924 Policard observed the selective localization and fluorescence of porphyrins in experimental tumours. In 1942, Auler and Banzer in Berlin confirmed the specific uptake and retention of haematoporphyrin in animal tumours and for the first time demonstrated its photodynamic action. Schwartz reported in 1955 that haematoporphyrin was a crude, variable mixture of many different porphyrins and isolated a more active component called haematoporphyrin derivative (HpD) (8).

Benzoporphyrin derivative

Benzoporphyrin derivative (BpD) is a chlorin compound with a maximum absorption peak of 690 nm, which gives as much as 50% greater penetration relative to the 630 nm wavelength used for porfimer sodium. BpD accumulates rapidly in tumour tissue, allowing optimal photoactivation 30-150 min following intravenous administration, and is rapidly cleared so that skin photosensitivity lasts a few days only. BpD is currently in phase I-II trials for the treatment of cutaneous lesions. Benzoporphyrin derivative (BpD) is a chlorin compound with a maximum absorption peak of 690 nm, which gives as much as 50% greater penetration relative to the 630 nm wavelength used for porfimer sodium. BpD accumulates rapidly in tumour tissue, allowing optimal photoactivation 30-150 min following intravenous administration, and is rapidly cleared so that skin photosensitivity lasts a few days only. BpD is currently in phase I-II trials for the treatment of cutaneous lesions.(9)

Meso-tetra-(hydroxyphenyl-chlorin)

Meso-tetra-(hydroxyphenyhl-chlorin) (mTHPC) is a chlorin compound with maximum activation at 652 nm. mTHPC has a high rate of photobleaching, which enhances the tumour: normal tissue therapeutic ratio, has a high extinction coefficient, good tumour selectivity and mild skin photosensitivity lasting 3-10 days. In the treatment of malignant mesothelioma a light dose of 10 J/cm’ produced a 1 cm depth of tumour necrosis when irradiated 48 h after the intravenous administration of 0.3 mg/kg of mTHPC. The concentration of mTHPC was up to 14 times higher in the tumour than in normal tissues. (10)

Mono-L-aspartyl chlorine

Mono-L-aspartyl chlorin e6 (NPe6) is a chlorin derived from chlorophyll-a. NPe6 has a peak of absorption at 664 nm, is maximally effective with a drug-light interval of 2 h and appears to have a predominately vascular effect with very little skin sensitization (11).

Phthalocyanines

Phthalocyanines are synthetic porphyrins with a maximum absorption in the 675-700 nm range. They have been chelated with aluminium and zinc which enhance their phototoxicity. In addition the less sulfonated compounds are the more active photosensitizers. The skin photosensitivity produced by phthalocyanines is less than that produced by porfimer sodium (11).

Endogenous photosensitization

5-aminolaevulinic acid (ALA) PDT is a novel method of PDT which utilizes the haem synthesis pathway, present in every energy producing cell, by which haem is synthesized from glycine and succinyl CoA. The rate-limiting step in the pathway is the conversion of glycine and succinyl CoA to aminolaevulinic acid, which is under negative feedback control by haem. Excess exogenous ALA, however, can bypass this control point and produce a build up of protoporphyrin IX (PplX), the photosensitizer, which when photoactivated produces the photodynamic effect (12).

Newer photosensitisers

The problems encountered with the haematoporphyrin derivatives have led to a search for drugs with a shorter duration of cutaneous photosensitization, activation by more penetrating longer wavelengths and better tumour to normal tissue drug ratios. The ideal photosensitizer for PDT should be a single pure compound that is non-toxic and should have a short half-life, specific binding to tumour, high quantum yield of singlet oxygen and an activation spectrum between 700 and 800 nm. Photosensitizers of differing properties may be used in combination to produce a synergistic effect (6).

Light sources and delivery

The first light sources used in PDT were conventional gas discharge lamps, whose output could be filtered to produce light of photoactivating wavelengths. However, such lamps produce significant heating of tissue and methods of light delivery are limited. Lasers have since become the most common source of light used for the photoactivation of photosensitizers used in PDT. Monochromatic laser light enables easier dosimetry, can be directed down a single optical fibre for endoscopic or interstitial illumination and a specific wavelength, particularly of more penetrating longer wavelength, can be chosen to match an absorption peak of the photosensitizer. The tunable argon-dye laser is the most commonly used system

as it can produce any wavelength from 350 to 700 nm and up to 3-4 W of effective light energy.(6)

The most efficient light source would match its output spectra to the activation spectra of the photosensitizer being used. As different photosensitizers are developed so different light sources are being developed to produce the ideal combination package.

Clinical Studies

Photodynamic therapy was studied in an animal model of Chemically-induced epithelial dysplasia and squamous cell carcinoma: PDT was performed 24 hours after i.v. injection of 2.5 mg/kg bw Photofrin, and using 100 J/cm 2 incident light at two activation wavelengths (514.5 nm or 625 nm). Two days after PDT, the majority of rats macroscopically showed a marked erythema of the entire palatal region. Microscopically all the rats showed oedema, haemorrhage, and necrosis of the epithelium of the intermolar area. The long-term results were not so favourable. No evidence of disease was found in 6 out of 20 rats in the 514.5 nm group and in 2 out of 20 rats in the 625 nm treated group. Epithelial dysplasia was found in 14 out of 20 rats in the 514.5 nm group, and in 18 out of 20 rats of the 625 nm treated group. Squamous cell carcinomas were found in 4 out of 20 rats treated with 514.5 nm and in 7 out of 20 rats in the 625 nm treated groups. Comparing both treatment wavelengths, better results were obtained in the 514.5 nm groups as this wavelength gave less normal tissue damage. (13)

The anti-tumor effect of photodynamic therapy (PDT) on mouse tumors was evaluated with bromodeoxyuridine (BrdU) immunohistochemistry. BrdU was injected into the mice intraperitoneally (40 mg/kg body weight). Immediately after injection of BrdU, PDT using a photosensitizing drug (hematoporphyrin oligomers: 20 mg/kg body weight) was carried out on the experimental group but not on the control group. BrdU labeling indices (LIs) of the tumor cells close to blood vessels and adjacent to the surrounding normal tissue were investigated. In the tumor cells close to blood vessels, the LIs of the experimental group were significantly lower than those of the control group. As for the tumor cells adjacent to the surrounding normal tissue, the LIs of the experimental group were similar to those of the control group. Thus, the effect of PDT was significant in the tumor cells close to the blood vessels, while the tumor cells adjacent to the surrounding normal tissue resisted PDT.(14)

A new therapy for the treatment of oral leukoplakia by 5- aminolevulenic acid (ALA) and photodynamic therapy (PDT) is presented. ALA, a precursor in the biosynthesis of haeme, induces the production of the endogenous photosensitizer protoporphyrin IX which can be used for PDT. Twelve patients, who had been suffering from leukoplakia of the oral mucosa for several years, were treated by ALA-mediated PDT. ALA was used as a topical photosensitizer and 20% ALA cream was applied to the leukoplakia lesion of the oral mucosa for two hours and then light activated at 630 nm, 100 mW/cm 2 and 100 J/era 2. Five patients showed complete response to the treatment, four patients showed a partial response and in three patients treatment was unsuccessful. One patient with partial response was retreated, after which the lesion disappeared. (15)

Eighteen patients with long-standing, bilateral, and severe OLP of the bucCal mucosa participated in the investigation. A dose of 0.6 mg/kg 8-methoxypsoralen was administered orally 2 hours before long-wave ultraviolet light irradiation was done. The patients were randomly assigned to treatment of the left or right side of the buccal mucosa. The irradiation therapy was given 12 times at intervals of 2 to 3 days, and the patients received a total average dosage of 16.5 J/cm 2. The results showed that 13 treated sites compared with six control sites responded significantly favorably to PUVA therapy. Two patients dropped out because of side effects that were similar to those seen after whole-body irradiation PUVA treatment. The follow up time was 12 months and concluded that PUVA seems to be effective in the treatment of OLP and should be considered in severe cases of OLP. (16)

Photodynamic therapy (PDT) is an effective method for *Candida* spp. inactivation in vitro and in vivo, but as yet, no clinical trial has been conducted. Five subjects with clinical and microbiologic diagnosis of DS were submitted to 6 sessions of PDT 3 times a week for 15 days. In each session, patients' dentures and palates were sprayed with 500 mg/L Photogem, and, after 30 minutes of incubation, irradiated by light-emitting diode light source at 455 nm (37.5 and 122 J/cm2, respectively). Cultures of *Candida* spp. from dentures and palates and standard photographs of the palates were taken at baseline (day 0), at the end of the treatment (day 15), and at follow-up time intervals (days 30 and 60). Four patients showed clinical resolution of DS (no inflammation) after PDT sessions, and only 1 subject demonstrated reduction in palatal inflammation. Recurrence of DS was observed in 2 patients during the follow-up period. PDT appears to be an alternative treatment for DS.(17)

170 patients with 226 lesions are treated with PDT. From those lesions, 95 are primary neoplasms, 131 were non-primaries (recurrences and multiple primaries). The overall response rate is 90.7% with a complete response rate of 70.8%. Subgroup analysis identified oral tongue, floor of mouth sites with more favourable outcome. PDT has more favorable results with certain subsites and with previously untreated lesions and suggested that, PDT can find its place for treating lesions in previously treated areas with acceptable results. (18)

Guglielmi (19) conducted a study was to assess photodynamic antimicrobial chemotherapy (PACT) via irradiation, using a low power laser associated with a photosensitization dye, as an alternative to remove cariogenic microorganisms by drilling. Remaining dentinal samples in deep carious lesions on permanent molars (n = 26) were treated with 0.01% methylene blue dye and irradiated with a low power laser (InGaAIP - indium gallium aluminum phosphide; λ = 660 nm; 100 mW; 320 Jcm(-2); 90 s; 9J). Samples of dentin from the pulpal wall region were collected with a micropunch before and immediately after PACT and kept in a transport medium for microbiological analysis. Samples were cultured in plates of Brucella blood agar, Mitis Salivarius Bacitracin agar and Rogosa SL agar to determine the total viable bacteria, mutans streptococci and Lactobacillus spp. counts, respectively. After incubation, colony-forming units were counted and microbial reduction was calculated for each group of bacteria. PACT led to statistically significant reductions in mutans streptococci (1.38 log), Lactobacillus spp. (0.93 log), and total viable bacteria (0.91 log) and they suggested that this therapy may be an appropriate approach for the treatment of deep carious lesions using minimally invasive procedures.

Conclusion

PDT is essentially a very simple concept and yet offers the possibility of an effective, specific method of destroying malignant, premalignant and benign tissues. There are now data to confirm that PDT can be curative in superficial dysplasias and tumours of the skin and aerodigestive tract. PDT offers tumour selectivity and control of effect by virtue of drug and light doses, is minimally invasive and yet allows treatment of a variety of disease sites with fibreoptic delivery of light. There is no evidence of cumulative toxicity or interaction with other treatment modalities so that it is helpful in the management of disease recurrence. In addition PDT has a favourable side-effects profile and allows day case treatment in many cases.

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