Clinical Applications of Photodynamic Therapy

Zastosowania kliniczne terapii fotodynamicznej

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Abstract
Photodynamic therapy (PDT) is a combined method of treatment of numerous malignancies as well as of non-oncological disorders. The procedure involves application of photosensitizing drug called photosensitizer, and its subsequent activation by the light of proper wavelength and energy dose. The most commonly used up-to-date photosensitizers are porphyrins and their derivatives: hematoporphyrin derivative, its purified product commercially known as photofrin II and texaphyrin. The other group of potent tumor photosensitizers comprises chlorins, e.g. meta-tetrahydroxychlorin, chlorin e6 and bacteriochlorin family. In the present paper, clinical applications of photosensitizers used in photodynamic therapy are discussed (Adv Clin Exp Med 2004, 13, 2, 359–365).

Key words: photodynamic therapy, photosensitizers, clinical applications, oncology.

Streszczenie

Słowa kluczowe: terapia fotodynamiczna, fotouczulacze, zastosowania kliniczne, onkologia.

Photosensitizers

Until the present moment a vast number of photosensitizers have been used both in pre- and clinical applications. Since the late 1970s when the first clinical trials with hematoporphyrin derivative (HpD) were done at Roswell Park Memorial Institute, in Buffalo, several hundreds of compounds were tested for in vivo activity. The photosensitizer given parenterally, i.e. intravenously or intraperitoneally is transported with blood stream to tissues [1]. Its accumulation in tumor tissue is, however, much higher than that in healthy organs like liver, kidneys, brain and skin [2, 3]. This selective accumulation in the neoplastic tissues is time-dependent. In the case of chlorin e6, maximum concentration was found as early as 3 hours after injection and tends to be very stable within the next 48–72 hours [4]. Maximum levels of photofrin II in tumors were observed 24 hours after injection, and for hematoporphyrin derivative this usually takes 24–48 hours [5]. Recently, a porphyrin precursor, delta-aminolevulinic acid (ALA), gained much interest, because it can be used in a very simplified modes, topically, and with less significant and harmful side-effects. ALA has been administered, e.g. as the ointment on eucerin support. After accumulation in altered tissue it metabolizes to protoporphyrin IX (PPIX) which acts as natural photosensitizer, although ALA is being also used in inhalation and orally [5]. Figure 2 shows the pathway by which ALA is being converted to PPIX.
Maximum concentration of PPIX in tumor was found after 4–6 hours following ALA application, whereas in the skin, after 3 hours [6]. Among many compounds used in the past in terms of photodynamic therapy (PDT) were: phthalocyanines [7], porphycenes [8], synthetic porphyrins [9] and others. Some critical properties for potent tumor photosensitizers were concisely outlined by Bonnett et al. [10]. The most important features are: low dark toxicity, high quantum yield of the triplet state of photosensitizer, high energy transfer from the triplet state to generate singlet oxygen, chemical homogeneity and stability, absorption in the red region of spectrum and selective accumulation in tumor and shorter time of retention in the whole body [10].

**Light Sources**

The choice of a proper light source to be applied in PDT is based on two principles. First, longer light wavelengths penetrate tissues better than shorter. The best photodynamic effects observed so far are in the range from 600 nm to 700 nm of light [11]. Second, in the red band, selection of the proper light wavelength depends on spectroscopic characteristic of photosensitizing drug with maximum absorption being different for particular compounds, e.g. for photofrin II and ALA – 630 nm and phthalocyanines – 675 nm.

Lasers are most often and widely used light sources in PDT. These are low energy devices, called soft lasers. Argon ion pumped dye [12],

![Fig. 1. The scheme of photodynamic therapy and diagnosis](image1)

**Fig. 1.** The scheme of photodynamic therapy and diagnosis

**Ryc. 1.** Schemat terapii fotodynamicznej i diagnostyki fotodynamicznej

![Fig. 2. The scheme of 5-aminolevulinic acid metabolism within the cell](image2)

**Fig. 2.** The scheme of 5-aminolevulinic acid metabolism within the cell

**Ryc. 2.** Schemat metabolizmu kwasu 5-aminlewulinowego w komórce
krypton [13], Helium-Neon [13], gold-vapor [14] and pulsed KTP (titanium-potassium phosphate), [12] lasers belong to willingly applied sources. The role of lasers and photodynamic therapy in the treatment of cutaneous malignancies has recently been reviewed [15].

In numerous clinical studies lasers were replaced by non-laser devices, like tungsten, xenon, halogen lamps [16] and light-emitting diodes [17].

In general, the PDT is based on photosensitizer application and its activation by proper light [18], and Figure 1 shows the principles of PDT and photodynamic diagnosis (PDD).

**Physicochemical Bases of PDT**

Upon accumulation in tumor tissue (and tumor cells as well) and irradiation with the proper light, the photosensitizer initiates a number of photochemical reactions. There are three various mechanisms described in tumor cell during PDT [19].

Type I (TO) results in formation of highly reactive free radicals, whereas in type II (TT) the mechanism of PDT is based on effects caused by singlet oxygen. Singlet oxygen is formed as a result of reaction between excited photosensitizer in triplet state and molecular oxygen in the ground state [19, 20]. The third type of reaction was called MTO and this assumed that free radicals generated in situ in tumor cells react directly with excited photosensitizer in triplet state. Such mechanism is known as triplet-doublet interaction [20]. The quantum yield of singlet oxygen formation varies between compounds: for PPIX it is 0.56, for photofrin II – 0.89, chlorin e6 – 0.64 and aluminum sulphonated phthalocyanine – 0.38.

Photochemical reactions which are present during the photodynamic process are as follows:

1. sens + h ν → 1sens (absorption)
2. 1sens → sens + h ν (fluorescence)
3. 1sens → sens (non radiation “decline”)
4. 1sens → 3sens (“intersystem crossover”)
5. 3sens → sens + h ν (phorescence)
6. 3sens + O_2 → sens + 1O_2 (energy transfer)
7. 1O_2 → O_2 (singlet oxygen “decline”)
8. 1O_2 + sub → sub_ox (substrate oxidation and cell death),

where: sens – photosensitizer ground state, 1sens – excited singlet state, 3sens – excited triplet state, 1O_2 – oxygen ground state, 1O_2 – oxygen excited singlet state.

There is a strong evidence that during PDT the mechanism may turn from type II to type I reactions. The action of singlet oxygen and free radicals on cellular level leads to damage of certain structures. As the main targets, cellular membranes, mitochondria and lysosomes are being affected and in some circumstances, the nuclei. This results in cell death. It has to be emphasized that hydrophobic sensitizers exert action directly on tumor cells, whereas hydrophilic compounds act indirectly via blood vessels endothelia. Blood vessels are injured at the time of PDT and thus the oxygen supply to tumor cells is disrupted.

**Clinical Applications of Photodynamic Therapy**

The clinical applications of PDT can be divided in two main areas, i.e. oncological and non-oncological. The latter comprises:

1. Inactivation of microbia – several studies showed that photosensitizers may kill Gram-positive and Gram-negative [21] bacteria. Exemplary, ALA inactivates *Haemophilus parainfluenzae* upon light treatment [22].
2. Psoriasis – PDT was successfully used alternatively to psoralen + UVA [23].
3. Barrett’s esophagus – in the treatment of this disease (photofrin II in the dose 2 mg/kg body weight (b.w.) or ALA (60 mg/kg b.w.) followed by light at the doses from 100 to 200 J/sq cm) the excellent results were achieved. The complete or at least partial remission of metaplastic epithelium in the lower third of esophagus was observed [24].
5. Arteriosclerotic plaques – recanalization of blood vessels.
6. Inactivation of viruses (e.g. HIV) in the blood and blood products.
7. Rheumatoid arthritis.
8. Skin diseases [25].

Oncological applications of PDT are more numerous and the properties of photosensitizers to fluoresce upon photoactivation with UV light have been exploited to localize very small tumors in patient body. In certain locations, like e.g. in urinary bladder, the effectiveness of PDT to visualize tiny, malignant tumors is higher than that of any other diagnostic procedure including MRI, USG or routine cystoscopy.

**Urinary Bladder Tumors**

The main aim of PDT in this location is the total eradication of both cystoscopically visible and invisible lesions and prevention of tumor
recurrences after transurethral resection (TUR). PDT has showed to be most effective in the treatment of superficial tumors, however the optimum results were achieved only after illumination of the whole bladder wall [26].

Some side-effects were observed after PDT in urinary bladder: transient skin photosensitivity, bladder retraction, temporary loss of capacity and in single cases, persistent bladder constriction. Stenzl et al. [27] treated 6 patients with superficial in situ cancer of the bladder after BCG therapy. The patients were given 0.5% ALA solution directly to bladder, followed by light irradiation. Control examination after 6 weeks, and later every 3 months, revealed the complete tumor remission in 5 patients, while in one case the recurrence occurred 10 months after PDT. Some side-effects, like dysuria or pollakisuria were found to be less frequent after ALA-PDT than after photofrin II PDT.

**Genital Tract Tumors**

PDT has been used to treat 13 patients with endometrial adenocarcinoma (FIGO stage – IA; G1-2) and cervical squamous cell carcinoma (G1-2). The complete remission has been achieved in 8 patients, partial in 2, whereas in only 3 cases no improvement was found [28]. In the course of more than ten years studies, Italian researchers treated with PDT 26 patients with locally recurrent genital tract tumors. They obtained 66% complete response rate of objectively stated symptoms and over 70% of cytologically and/or histologically negative biopsies.

**Brain Tumors**

There is solely a small number of contributions dealing with PDT in this location. Photosan 3, which is another commercial name of photofrin II, and argon laser were used to treat multiform glioblastoma with complete responses obtained in single cases [29].

**Lung and Bronchial Tumors**

In 1980, PDT was used for the first time to treat lung cancer. This therapy offers some advantages over routine methods because it requires minimally invasive techniques, can be repeated for several times, and except for skin photosensitivity, it does not evoke any significant side-effects. Up to the present moment PDT has been involved in more than 5500 cases of lung cancer in the world. Most often applied photosensitizers were HpD and photofrin II in doses 2–5 mg/kg or 1–2 mg/kg, respectively. Total light doses varied from 100 to 200 J/sq cm to treat mainly the early lung cancer [30]. In Mayo Clinic, USA, 13 patients were subjected to PDT and in 12 cases the total tumor response has been achieved after single or double PDT. In 3 of those 12, the recurrences occurred within two years following therapy, although they were succesfully treated later by routine surgery or repeated PDT [31]. In turn, Kato et al. [32] used Photofrin-PDT to eradicate 29 lesions in lung cancer patients obtaining over 80% of complete responses! The effects of PDT strongly depend on size of the primary tumor. In spite of this, even in large, obturative bronchial tumors some promising
results were recorded. In this location, the ALA has also been used to treat malignant bronchial stenosis [33]. Unfortunately, in large tumors the frequency of side-effects of PDT increases. The most common complications were: massive hemoptysis and respiratory distress syndrome. In the group of 26 patients Sutedja et al. [34] observed 4 cases of lung hemorrhages within 1.5 to 6 months after PDT, however they did not ascribe those failures to PDT. The other side-effects like bronchial edema or obturation were less frequent.

Upper Aerodigestive Tract Tumors

In this location PDT was applied in the treatment of both malignant and benign laryngeal tumors (laryngeal papillomas). Since 1982, when PDT was used for the first time to cure local recurrences of laryngeal cancer, the number of contributions dealing with these tumors constantly increases. In the therapy of unilateral vocal cord cancer, 72% of tumor complete response rate was achieved [35]. In the studies recently performed in Poland, the positive effect of PDT on pre-cancerous lesions in vocal cords has also been confirmed [36]. Complications encountered after PDT in this location comprise: aerodigestive tract lumen constriction and fistula formation after HpD-PDT, however these disadvantages could be overcome by applying photofrin II. Several cases of laryngeal and hypopharyngeal cancers have also been successfully treated in Poland [37].

Skin Tumors

There is a wide range of methods of treating skin disorders, however they reveal numerous drawbacks, like e.g. unsatisfactory cosmetic effects or failures in treatment of multiple tumors. In the past, during the last 12 years, PDT has been involved in therapy of a number of skin cancers, like basal-cell carcinoma, BCC, squamous-cell carcinoma, SCC, [38], Bowen’s disease [39], recurrent breast cancer and Kaposi sarcoma [40]. In single studies, it has also been used to palliative treatment of malignant melanoma metastases. In the therapy of BCC numerous photosensitizers were applied, initially exogenic photofrin II, HpD or Nile blue derivatives, but recently ALA gained very much interest. ALA may be applied directly onto the skin lesions, so that the selectivity of treatment is high and general skin photosensitivity can be avoided. ALA metabolizes in the lesion to protoporphyrin IX which acts as the photosensitizer. In literature, there is a wide spectrum of positive effects of PDT reported so far in skin disorders, what undoubtedly depends on treatment protocols and criteria of patients selection. In 1990 ALA-PDT was used topical for the first time in the world. They applied 20% ALA solution in water-oil emulsion and 3–6 hours later irradiated the lesions with light from Kodak slide projector equipped with 500 W lamp (the total light doses varied from 15 to 150 J/sq cm). They obtained 90% of complete response rate. Two years later they confirmed positive effects of PDT in 300 lesions of BCC type with complete tumor response rate as high as 79%. In other study, Warloe et al. [41] used ALA-PDT to treat 96 BCCs in 11 patients gaining 96% of complete responses with excellent cosmetic results. Svanberg et al. [42] obtained 100% cure rate of 55 superficial BCCs and 90% in Bowen’s disease. ALA-PDT can also be successfully used in therapy of skin T-cell lymphoma [43]. Koderhold et al. [44] proved the effectiveness of Photosan 3-PDT in therapy of penile Queyrat disease.

The authors’ efforts in treatment of skin malignancies, like e.g. BCC and SCC resulted in very promising effects. Briefly, more than 30 cases of skin tumors (BCC, SCC, Bowen’s disease) were treated with topical ALA-PDT and the final score was 100% of complete tumor responses [45]; see figures 3A i 3B.

References


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