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The role of photodynamic therapy as a novel strategy in clinical practice

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ABSTRACT

Photodynamic therapy (PDT) is a novel non-invasive form of light therapy. PDT can be widely applied in various fields of clinical approach, particularly in the treatment of dysplastic conditions and malignant tumours of the brain, gastrointestinal tract, respiratory and reproductive systems. PDT is most frequently utilised in oncological dermatology; however, it could be easily used in the treatment of acne, skin mycosis or viral infections, e.g. HSV infection. The mechanism of PDT is based on the irritation of a chemical, a so-called photosensitizer that was selectively accumulated in a particular pathological tissue, by the light. The outcome of this irritation is a photochemical reaction that transform the photosensitizer into an active toxic substance that destroys the non-functional cells. The advantages of PDT include high efficacy and selectivity, the possibility of multiple administration of light doses and no evident contraindications of simultaneous usage of PDT and other therapeutic methods in patients of various clinical conditions. Moreover, virtually none side effects and excellent cosmetic effects are making PDT a very well tolerated therapy for many patients. Further steps are taken to introduce PDT in the treatments of cardiovascular disorders, e.g. atherosclerosis, eye disorders or photojuvenation of the skin.

***Keywords*:** Photodynamic therapy, PDT, light therapy, light delivery, cancer, photosensitizer

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1. INTRODUCTION

Photodynamic therapy (PDT) is a fast-developing form of light therapy used in the treatment of both oncological and non-oncological conditions. PDT brings the possibility of selective destruction of inflamed or neoplastic cells located in the skin or the mucosa. PDT can be applied in such clinical fields as dermatology, oncology, gynaecology and dentistry. The qualities such as non-invasiveness, promising therapeutic outcomes and no contraindications to use in synergy with other treatment methods, are placing PDT within the growing group of possible applications in medicine.

The aim of this review is to explore the background of PDT and summarise its application in current clinical practice.

2. THE ROOTS OF PHOTODYNAMIC THERAPY

The history of light therapy dates back to the ancient times. [1] Thousands of years ago, the Egyptians, followed by the Romans later on, used natural sunlight to cure medical conditions. The historic name of light therapy, i.e. heliotherapy, has its stems in ancient Greece and refers to sunlight, thus pointing out the fact that light therapy was known and recognized by ancient civilisations. [2] Despite the lack of scientific understanding underpinning it, light therapy continued to be practiced and made its way up to contemporary medicine. The advancements that came around made it possible for many medical conditions to be treated systemically using well researched pharmacology. This fact has contributed to a decrease in the interest in heliotherapy as a form of routine treatment method. Another factor to light therapy's thinning popularity was the fact that very little research was conducted as to the biological mechanisms evoked in the response to light exposure, both for white light and other wavelengths. It was not until the break of XIX and XX century that related fields of science, such as biophysics, yielded enough scientific support to bring heliotherapy back in the arsenal of clinical treatment methods.

In 1893, Danish general practitioner Niels Finsen, dubbed "the father of modern light therapy", constructed an arc lamp and successfully used it to cure skin tuberculosis. In 1903, he was awarded Nobel Prize for his contribution to medicine by skin treatment using light rays. [3] In 1897, Herman von Tappeiner and colleagues observed the cytotoxic effect of certain pigments in microorganisms exposed to light. In 1903, he and others used eosin as a photosensitizer to cure skin cancer. Tappeiner coined the term "photodynamic reaction" to describe the interaction between a photosensitive compound and light radiation in living tissues. [4] The PDT research conducted through XX century focused mainly on refining the methodology, searching for novel photosensitizer candidates and experimenting with different light wavelengths. A certain clinical trial, conducted by T. D. Dougherty in 1978, turned out to be a true milestone in the development of photodynamic therapy. The trial involved a cohort of 113 people, 111 of which showed promising results including total or partial remission of the disorder after light therapy. [5]

For many following years, PDT was applied in gradually increasing number of cancer types. Presently, experimental and clinical work concerning PDT in various fields of medicine, both *in vitro* and *in vivo*, continue to be conducted in many facilities worldwide.

3. MECHANISM OF ACTION OF PDT

The mechanism of action of photodynamic therapy requires simultaneous presence of three components, i.e. a photosensitizer that localizes in pathologically altered tissue and predisposes it to light exposure toxicity, a light source of specific wavelength that activates the photosensitizer and oxygen molecules dissolved within the tissue. The photosensitizer, administered systemically or locally, is taken up by all cells regardless of their condition. However, healthy cells excrete it within hours following the administration, whereas pathologically altered cells keep it inside up to a couple days. [6] The reason behind this phenomenon lies in the property of the photosensitizer – namely, it tends to be retained by cells of pathologically high metabolic rate and proliferating in an uncontrollable manner, such as cancerous cells. Due to the radiation of light of specific wavelength adjusted to the absorptive properties of the photosensitizer, the latter becomes activated and passes the energy acquired from light to surrounding molecules. This photodynamic reaction results in excitation of oxygen molecules and thus production of free radicals (ROS – *reactive oxygen species*) that randomly oxidize all the cell components and lead to its death. [7]

4. PHOTOSENSITIZERS AND LIGHT SOURCES USED IN PDT

The most frequently used photosensitizers are porphyrins and their precursors, e.g. 5-aminolevulinic acid (5-ALA) – a physiological component of haem biosynthesis pathway. Photosensitizers can be administered systemically (internally), either orally or intravenously, or locally (externally), depending of the type of targeted pathology. 5-ALA, administered locally in a form of an emulsion or an ointment, is frequently used in dermatology. [8] Following a couple of hours after application, the pathologically altered site can be exposed to light. Depending on the thickness or depth of the altered site, different wavelengths of light, either within red or blue spectrum, can be used to ensure proper penetration of the targeted site. Red light is characterised by a relatively long wavelength (635 nm), thus it penetrates the skin deeper and can be used to treat neoplastic lesions. Blue light, however, is of a shorter wavelength (470 nm) and can be used to treat pathologies localised in superficially in the skin. [9]

The light sources used in PDT to activate the photosensitizer can be coherent or non-coherent and include lasers, light-emitting diodes (LED), lamps equipped in proper filters and halogen lamps. [10]

5. CLINICAL APPLICATIONS OF PDT

In contemporary medicine, photodynamic therapy enters subsequent fields of applications. It is considered a very promising treatment method due to its high specificity. Nonetheless, the clinical guidelines and procedures concerning PDT are scarce.

5. 1. DERMATOLOGICAL CONDITIONS

Photodynamic therapy has been broadly used in dermatology to treat non-oncological lesions, as well as dysplastic lesions and early neoplasms. PDT is most predominantly recommended for dysplastic lesions of the skin and mucosa: keratinisation due to sunlight, Bowen's disease and leucoplakias. Moreover, PDT has been applied in superficial skin

cancers – basal-cell carcinoma (BCC) and squamous-cell carcinoma (SCC). [11] PDT is particularly effective in the treatment of BCC where in 90% of the cases a total remission was observed. [12] Other than that, PDT has been used to cure actinic keratosis [13] [14], common skin warts [15], acne [16] and psoriasis [17].

5. 2. APPLICATION IN ONCOLOGY

As a consequence of penetration limitations due to physical dispersion of light in subsequent tissues, photodynamic therapy is most effective in lesions localised superficially. It yields most effective results in neoplasms that are easily accessible by endoscopic examination, e.g. bladder cancer, prostate cancer, and tumours localised in the upper respiratory system or gastrointestinal tract. Additionally, PDT can be used as a diagnostic method (photodynamic diagnosis, PDD), e.g. intraoperatively, using optical fibres inserted into the tumour mass. [18] This way the targeted focus can be visualised when it is not visible in a macro scale. Photodynamic therapy has also been reported to yield significant results in brain tumours treatment. Over the course of recent years, PDT has been acknowledged as a safe and selective method to extend patients survival and increase their quality of life. It has been reported that patients treated with synergic treatment (surgery and PDT) tend to live longer than those treated only surgically. [19] [20]

5. 3. GYNAECOLOGICAL CONDITIONS

In gynaecology, photodynamic therapy application spans from the treatment of chronic inflammations such as lichen sclerosus [21] to conditions of viral aetiology such as genital warts. The photodynamic method is also effective in the therapy of cervical dysplasia and pre-invasive lesions of vulva and reproductive organs. [22]

5. 4. OPHTHALMOLOGIC CONDITIONS

In ophthalmology, photodynamic therapy has been applied using red light of 690 nm wavelengths by the means of an ophthalmoscope. It has been of most efficacy in the treatment of age-related macular degeneration. [23]

5. 5. PDT IN DENTISTRY

In stomatology, photodynamic therapy serves as a method of treatment of local bacterial infections of periodontium. Conventionally, such conditions are treated with antibiotic therapy supported by mechanical removal of bacterial plaques formed on teeth. Such methodology can cause increased bacterial resistance to antibiotics. [24] PDT eliminates the necessity of antibiotics administration and facilities stomatological treatment. It can be utilised in the treatment of mucosal leucoplakias of dysplastic origin. [25]

5. 6. OTHER APPLICATIONS

Photodynamic therapy has also germicidal properties. Specific photosensitizers such as methylene blue or rose bengal can be toxic to certain bacterial or fungal strains, e.g. *Streptococcus* or *Candida*. [26] Research indicates high efficacy of PDT against protozoan or viral infections. PDT has been reported to have inactivated viruses such as HIV [27], HPV and HSV [28] in *in vitro* studies and clinical trials.

6. CONCLUSIONS

Photodynamic therapy is a promising method in the treatment of cancer and other diseases. It is possible that it becomes an alternative tool for many routinely applied anti-cancer therapies. PDT, being a non-invasive method, does not require anaesthesia. The mildness of side effects associated with PDT, e.g. erythema, oedema and short inflammation, and most importantly the fact that it does not result in scar formation, makes PDT a readily accepted method by patients. On the top of that, PDT can be used in synergy with other treatment methods, e.g. chemotherapy and radiotherapy; and regardless of the clinical condition of a patient.

Despite intense research, the exact mechanisms of photodynamic therapy remain largely unknown. Nevertheless, due to its great diagnostic and therapeutic potential, the results of research focused on PDT are received with a lot of excitement and encourage to continue to further improve this method.

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