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Original Theoretical Research

Photodynamic Therapy: The History of Formation and Development of the Neoplasm Treatment Method

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Abstract

At present, there exist many examples of successful implementation of photodynamic therapy in treatment of tumours of various localizations, as well as skin neoplasms and infectious diseases in both humans and animals. The article traces formation and development of the photodynamic therapy, shows the influence of the type of photosensitizer and the dose of radiation applied on the efficiency of treatment, it emphasizes the potential of this method due to its low invasiveness and ability to minimize side effects.

Keywords: photodynamic therapy, photosensitizer, irradiation, tumour, neoplasm, laser

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Оригинальное теоретическое исследование

Фотодинамическая терапия: история становления и развития метода лечения новообразований

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Аннотация

На сегодняшний день фотодинамическая терапия насчитывает большое количество примеров успешного применения при лечении раковых опухолей различной локализации, а также кожных новообразований и инфекционных заболеваний как людей, так и животных. В статье прослежен путь становления и развития фотодинамической терапии, показано влияние вида фотосенсибилизатора и дозы применяемого излучения на эффективность лечения, подчеркнута перспективность метода вследствие его низкой инвазивности и способности минимизировать побочные эффекты.

Ключевые слова: фотодинамическая терапия, фотосенсибилизатор, облучение, опухоль, новообразование, лазер

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Introduction. Development of the innovative efficient treatment of neoplasms is an important objective both for human and veterinary medicine, since cancer remains an acute problem despite significant scientific advances in the field of tumour diagnostics and treatment. One of the advanced and forward-looking approaches to treatment of oncological, as well as skin and infectious diseases, is photodynamic therapy (PDT), a method characterized by safety,

non-toxicity, minimal immune suppression, and low invasiveness [1]. From the molecular perspective, the efficiency of PDT depends on three pivotal factors necessary for a chemical reaction [2]:

1. Photosensitizer — a chemical substance capable of becoming active and generating reactive oxygen species that act on cells, when exposed to light of a certain wavelength. Photosensitizers can be organic or inorganic chemical compounds.

2. Light of the appropriate wavelength — to activate the photosensitizer, it is necessary to use light of a certain wavelength that corresponds to the absorption spectrum of the photosensitizer. The most commonly used light sources are a laser or a LED.

3. Dissolved oxygen in cells — the presence of oxygen in cells is essential for PDT efficiency, since the process involves activation of the photosensitizer by light resulting in conversion of the oxygen in the cells into singlet oxygen, which then attacks and destroys cancer cells or pathogens.

The aim of the present article is to track the history of photodynamic therapy development by illustrating data on discoveries in this area and successful application of the method in treatment of humans and animals; to show the efficiency of PDT in comparison to traditional methods of treatment and to evaluate expediency of further research in this area.

History of photodynamic therapy formation and development. Treatment of diseases using photochemotherapy was first mentioned in the literature of Ancient Egypt, China and India. Even then, doctors used natural photosensitizers (without knowing this word) — psoralens contained in parsnip, parsley, St. John's wort, black seeds of Psoralena corylifolia — to treat vitiligo and psoriasis, and noticed that the compounds of these herbs could be activated when exposed to sunlight [3, 4]. Historical references to treatment of various diseases using the effect of sunlight on the human body (heliotherapy) can be found in the works of famous scientists of Ancient Greece, such as Herodotus [5].

A qualitative leap in the development of photodynamic therapy occurred at the end of the 19th century thanks to the Danish physiotherapist N. Finsen, who studied the effect of sunlight on living organisms. In 1893, Finsen published the results of his research on the use of red light in treatment of chickenpox that helped to prevent pus formation in blisters. In 1903, the scientist was awarded the Nobel Prize for his achievements in the field of photodynamics [6].

In 1900, in the laboratory of the Austrian pharmacologist H. von Tappeiner, the medical student O. Raab first discovered an oxygen-dependent photochemical reaction. He experimentally established that certain dyes in the presence of oxygen and sunlight are capable of causing rapid death of Paramecia cells: the paramecium died when exposed to a combination of acridine dye solution and daylight, and survived in the absence of the dye or in its presence in the dark [3, 4, 7].

In 1903, Tappeiner and A. Jezionek developed their own PDT technology and conducted the first treatment sessions for diseases such as lupus, psoriasis, and skin cancer. They used a 1% eosin solution as a photosensitizer, and performed the prolonged insolation or artificial irradiation by an arc lamp [3, 4, 7]. At the same time, Tappeiner introduced the terms “photosensitizers” and “photodynamic action” into the scientific vocabulary, which made it possible to separate this effect from the photochemical reactions observed in photography [8].

Over the following years, the photodynamic therapy method underwent significant changes and improvements related to the development of the first porphyrin-based sensitizers. In 1911, W. Gausmann conducted an experiment that showed that Paramecia cells die when exposed to the lamp light in growth medium composed of hematoporphyrin [9]. In 1912, this substance was first tested in the human organism: the German doctor F. Meyer-Betz injected himself with 200 mg of hematoporphyrin intravenously, which resulted in solar photosensitivity of the body expressed in the form of edema and hyperpigmentation lasted for about two months.

In 1924, the French researcher A. Policard conducted research on animals with malignant tumours, injecting them with hematoporphyrin and then irradiating the tumour area with ultraviolet light: malignant neoplasms fluoresced in the orange-red region of the spectrum — this effect could be explained by the presence of porphyrin proteins in tumour cells [11, 12].

In 1942, two scientists from Berlin, G. Banzer and H. Auler, decided to study and evaluate the process of accumulation and fluorescence of porphyrins administered exogenously into the body. They found red fluorescence after subcutaneous and intramuscular administration of hematoporphyrin in the primary tumour and in metastases in rats [13, 14], which indicated the accumulation of

hematoporphyrin both in primary tumours and metastases, as well as in the lymph nodes. Exposure to light gave positive results [15].

In 1948, the American scientist W. Figg and his colleagues conducted an experiment involving 240 mice with transplanted tumours, who were injected with various porphyrins: hematoporphyrin, protoporphyrin, coproporphyrin and zinc hematoporphyrin. Observations showed that within 24–48 hours all of the above substances accumulated in tumours. After this period, fluorescence persisted for 10–14 days [16]. However, the use of these porphyrins as photosensitizers for PDT was hindered by their severe cutaneous phototoxicity.

In the 1960s, R. Lipson conducted a significant study aimed at enhancing the action of hematoporphyrin in tumour tissue. The experiment implied treating hematoporphyrin with sulfuric and acetic acids, followed by alkaline hydrolysis. As a result, a hematoporphyrin derivative was obtained, which subsequently started to be applied in fluorescent diagnostics of various oncological diseases, including lung, cervical and gastric cancer [17]. In 1966, Lipson and his team successfully used this derivative to treat a female patient with a recurrent ulcerating tumour of the mammary gland, which recurred just a few weeks after the completion of a course of radiation therapy. This study was an important step in the development of methods of diagnostics and treatment of oncological diseases, opening up new horizons for the use of photodynamic therapy.

In 1966-1967, studies were conducted aimed at assessing the efficacy of various sensitizing agents, including methylene blue, which stood out of the rest. The results of the experiments demonstrated its superiority over previously used reagents. In particular, significant destruction of tumour tissues was noted, as well as successful healing of wounds caused by unwanted damage [18].

In 1974, the first drug for photodynamic therapy called “Photofrin I” was registered. The drug was obtained from a mixture of hematoporphyrins using the membrane filtration technique. In 1975, Professor T. Doherty, head of the Photodynamic Therapy Centre at the Cancer Research Institute in Buffalo (USA), successfully treated 50% of mammary tumours in mice and Walker256 carcinosarcomas in rats. In his experiment, he used "Photofrin I", which got accumulated in target tissues, and then was activated by the red light of xenon lamp using optical filters [16, 17].

Since 1978, photodynamic therapy has been widely used clinically in the field of oncology. T. Doherty published the results of successful application of PDT in 25 patients suffering from Basal and Squamous cell carcinomas, melanoma, as well as recurrent and metastatic tumours of the skin and mammary gland. Irradiation of neoplasms was carried out using a xenon lamp 24–160 hours after the administration of the photosensitizer [17]. Subsequently, this method of treatment began to be actively developed in Japan, Germany, China, France, Great Britain and other countries.

In the 1980s, Doherty and colleagues isolated an active fraction of hematoporphyrin, called "Photofrin II", which differed from "Photofrin I" in its better selectivity for accumulation in tumour tissues and a pronounced antitumour effect. For a long time "Photofrin II" remained the only photosensitizer approved for treatment of oncological diseases of the skin and mucous membranes in many countries [19, 20].

In 1985, a female scientist B. Henderson described damage to blood vessels that fed tumour cells during their growth and progression induced by PDT. This mechanism became one of the key aspects of tumour destruction when using this treatment method [21].

It should be noted that the development of the photodynamic therapy and the increase of its efficiency was significantly related to the development, implementation and use of lasers. In 1964, scientists N.G. Basov, A.M. Prokhorov and C.H. Townes were awarded the Nobel Prize in Physics for outstanding achievements in the field of quantum electronics. Their fundamental research became the basis for the creation of generators and amplifiers based on the laser principle. This research not only opened new horizons in physics, but also served as a catalyst for the development of various types of lasers, which subsequently found wide application in various fields of science, including medicine.

In 1986, the Research Institute for Laser Surgery of the USSR Ministry of Health was established in the Soviet Union, headed by Professor O.K. Skobelkin, a surgeon, Honoured Scientist of the RSFSR and the founder of laser medicine in the country. In his scientific activity, the professor focused on the research aimed at creating a domestic photosensitizer and developing a laser device for photodynamic therapy [22].

In the 1980s, at the Institute of Biophysics of the USSR Ministry of Health, under the supervision of Professor G.V. Ponomarev, the drug “Dimegin” was developed based on natural protohemin [23]. In 1990, at Moscow State Academy of Fine Chemical Technology named after M.V. Lomonosov, under the supervision of Professor A.F. Mironov, the first domestic photosensitizer “Photogem” was synthesized from the group of hematoporphyrin derivatives [24].

A quite well-known representative of porphyrinic photosensitizers is 5-aminolevulinic acid (5-ALA), a natural precursor of the endogenous photosensitizer protoporphyrin IX (PP-IX). It was first used in 1990 by the Canadian scientist J. Kennedy. The mechanism of action was based on the ability of tumour cells to accumulate photoactive protoporphyrin IX in the presence of exogenous 5-ALA [8].

In 1994, clinical trials of the second-generation photosensitizer “Photosens”, representing a sulfonated aluminum phthalocyanine, were completed at the State Research Center "NIOPIK" under the supervision of Professors E.A. Lukyanets and G.N. Vorozhtsov. Today, “Photosens” is successfully used to treat malignant tumours of various localizations due to its high biological activity: the drug demonstrates a strong absorption band in the red region of the spectrum with a wavelength of 670–675 nm. Later, under the same supervision, the drug “Alasens” was developed, based on 5-ALA and since then used in treatment of keratoses, Basal cell carcinoma, bladder cancer, brain tumours, and stomach tumours [13].

Due to the reason that first-generation photosensitizers based on hematoporphyrin derivatives had a number of disadvantages (they got slowly accumulated in tumour tissues, had a fairly low therapeutic efficacy, and at the same time a long period of after-treatment cutaneous phototoxicity, which significantly deteriorated the quality of life of patients), further research in this area was aimed at developing second-generation photosensitizers that would have a broad absorption band in the red region of the spectrum [25]. Currently, drugs based on 5-ALA are registered in Norway — Metvix (PhotoCure ASA), Canada — Levulan (DUSA Pharma), the Republic of Belarus - Alamin (Institute of Bioorganic Chemistry of the National Academy of Sciences of Belarus) [16].

In the period of 1994–2001, research was conducted in Russia to develop technologies aimed at extracting a complex of biologically active chlorins from herbal raw material, among which the main component was E6 [26]. In 2002, the company “Rada-Pharma” LLC, under the supervision of Candidate of Chemical Sciences A.V. Reshetnikov, synthesized the domestic photosensitizer “Radachlorin” based on chlorin E6. And in 2004, “Veta-Grand” LLC, under the supervision of Professor G.V. Ponomarev, synthesized “Fotoditazin” based on E6.

Today, the following chlorine derivatives are widely used in clinical practice: “Foscan” (Biolitec AG, Germany), “Verteporfin” (Novartis Pharma, Switzerland), “Taloporfin” or “Laserphyrin” (Japan) [26]. Using light waves of a certain length, they are capable of targeted impact on tumour cells and their destruction. The development of such drugs is of great importance for medicine and veterinary science and opens up new possibilities in treatment of complex diseases.

In 2001, a third-generation photosensitizer called “Photolon” was developed in Belarus at the Republican Unitary Enterprise “Belmedpreparaty”. The main distinction of drugs of this generation is the technology of mixing photosensitizer molecules with molecules of other substances, such as nanoparticles or liposomes, which enables to significantly enhance selectivity for accumulation of photosensitizer in tumour tissue. The drug “Photolon” is a molecular complex consisting of chlorine E6 salt and polyvinylpyrrolidone. Due to its unique structure and properties, “Photolon” is widely used in oncology, in particular, in treatment of skin cancer, mucosal cancer and precancerous conditions of the cervix. Studies show that the use of this drug helps to increase the efficciency of photodynamic therapy due to improved accumulation of the active substance in tumour cells and minimization of the impact on healthy tissues [16].

On December 29, 2012, by Order No. 1629 of the Ministry of Health of the Russian Federation, photodynamic therapy was included in the high-tech medical care list, thus, emphasizing the importance of this advanced method of treatment, which continues to be developed and integrated into clinical practice. Currently, the development of PDT is aimed at creating new drugs that efficiently absorb light in the spectral region known as the “therapeutic window” (700–900 nm). In this region, the absorption of light by biological tissues is minimal, which allows for deep penetration of light into the body tissues, significantly reducing potential harm from radiation and increasing the efficiency of therapy.

Experimental studies of exogenous photosensitizers of various classes, such as naphthalocyanines and phthalocyanines, chlorins, pheophorbides and their derivatives, as

well as benzoporphyrin derivatives and purpurins, are being actively conducted. These compounds have unique optical properties, which makes their use in PDT prospective [27]. Research is focused on assessing the efficacy of these photosensitizers in the context of their ability to cause photochemical reactions when irradiated with light in therapeutic window. The main attention is paid to improving the selectivity of the action of drugs on tumour cells and minimizing side effects for healthy tissues.

Significant progress in the field of photodynamic therapy is explained not only by the development of photosensitizers, but also by improvement of light sources used in the treatment process. In particular, laser diodes have gained wide popularity due to their unique physico-chemical properties, which enable more precise and efficient action on tumour tissues [28]. Various schemes and modes of using light sources for efficient PDT are being studied and improved. In parallel with this, photodynamic diagnostics (PDD) is developing, which makes possible more precise detection of cancer and planning its treatment using the fluorescence of activated photosensitizers [5].

In Russia, photodynamic therapy is practiced in various medical institutions, including specialized oncology centres, clinics and research institutes, where it is used to diagnose and treat oncological diseases. In addition, PDT is used in dermatology, dentistry, ophthalmology, cosmetology, gynaecology, as well as in treatment of inflammatory skin diseases and vascular disorders. Innovations in the field of PDT include its integration into other types of therapy, such as chemotherapy, radiation therapy and targeted therapy, which increases the efficacy of treatment and minimizes side effects [5, 23].

PDT demonstrates high efficiency in treatment of various types of cancer. For example, when using the photosensitizer “Photolon” in combination with cisplatin in rats with M-1 sarcoma, complete tumour regression was achieved in 89% of animals and its growth was inhibited almost in 100% of animals [29]. In studies on mice with Ca-755 mammary adenocarcinoma, laser irradiation with a wavelength of 687 nm showed an improvement in the therapeutic effect, while at a wavelength of 678 nm the efficiency decreased to 23% [30]. PDT also showed good efficiency in treatment of pharyngeal cancer, laryngeal cancer and early forms of oral cancer achieving high cure rates. In addition, the use of nanobody-photosensitizer conjgates induced significant regression of orthotopic tumours with high HER2 expression in mice [31].

In veterinary medicine, photodynamic therapy is especially useful when surgical intervention or chemotherapy are contraindicated due to the animal’s condition. In 2009, O.A. Kuleshova and S.A. Yagnikov conducted a study in which they used “Fotoditazin” to treat oral mucosa spontaneous tumours in domestic dogs and cats. A positive effect was achieved with a photosensitizer dosage of 1–2 mg/kg and a light energy dose of 300-600 J/cm² [32].

In 2012, at the Centre for Biology and Veterinary Medicine of RUDN and the Department of Experimental Therapy and Diagnostics of the N.N. Blokhin Russian Cancer Research Center of RAMS, the accumulation and distribution of the photosensitizer was studied to determine the therapeutic dose for diagnostic fluorescence and photodynamic therapy in dogs and cats with tumour lesions of the abdominal organs, oral cavity, lungs and brain. It was found that the therapeutic dose of the photosensitizer was 1 mg/kg of the animal’s body weight. The accumulation time varied: 90 minutes for tumours of the chest and abdominal regions and the brain; 150 minutes for tumours of the oral mucosa. At a light energy density of 200 J/cm², PDT has an anti-inflammatory activity, and at 300–400 J/cm² — therapeutic [33].

In 2013, E.V. Davydov used two types of photosensitizers in the combined treatment of tumours in small domestic animals: chlorin E6 intravenously and externally in the form of a gel, and then “Dimegin” in the form of a gel. The study proved high efficiency of treatment with complete tumour regression [34].

In 2016, V.I. Telpukhov and E.V. Davydov, using PDT before surgery in cats with soft tissue sarcoma, found that with this variant of treatment, the tumour became more operable [35]. Also in 2016, when treating spontaneous mammary tumours in cats using photodynamic therapy, a good result was obtained: “Fotoditazin” was used as a photosensitizer, and the radiation source had a wavelength of 660±2 nm and a power of 1.5W. Within 6–10 days the tumour necrosis and rejection was observed, and upon further observation, complete regression was noted in the animals [36].

The use of PDT as a preoperative or intraoperative treatment method has become a future-oriented direction of research. In 2017, E.V. Davydov and colleagues used PDT in the preoperative mode, followed by radical mastectomy in small domestic animals with spontaneous mammary tumours. In the experimental group, suture healing time was twice as fast, the process of lymphorrhea decreased and no complications were observed [37].

In 2022, R. Shrestha and colleagues investigated the efficacy of photodynamic therapy using pure chlorin E6 (Ce6) for treatment of tumours in dogs and in mouse tumour models. Five dogs with different cancer types were treated with Ce6-PDT one to two times, and two dogs also underwent Ce6 fluorescence guided imaging by means of photodynamic diagnostics (PDD). In two patients with mammary carcinoma and histiocytic sarcoma, tumours significantly decreased in size and health improved. The additional use of Ce6-PDD made it possible to reveal tumour lesions that were not visible under white light. In mouse models of melanoma and pancreatic cancer, Ce6-PDT also showed significant tumour reduction [38].

In 2023, Professor D. Lo and colleagues used dogs to evaluate the efficacy of gold nanoparticles targeting prostate-specific membrane antigen as a method for fluorescence imaging and PDT of prostate cancer. After administration of nanoagents (AuNPs-FS158) and PDT activation with laser radiation (672 nm), it was found that photoluminescence of prostate tumours significantly increased compared to normal tissue. PDT caused damage in irradiated areas to a depth of 1–2 mm, including necrosis and inflammation, while non-irradiated areas remained without visible damage [39].

Also in 2023, a case of treatment of Squamous cell carcinoma of the corneal limbus in a cow using surgical excision and PDT was described. After surgery, EmunDo® (infracyanine green) was applied to the operation site and the cornea was irradiated with a laser diode with a wavelength of 810 nm and power of 500 mW to a total energy of 167 J. Eleven months after surgery, only slight corneal fibrosis was observed without signs of tumour recurrence [40].

In 2024, L. Sebbag and O. Peter described a clinical case of treatment of two cats with Squamous cell carcinoma of the eyelid using marginal resection and photodynamic therapy. After surgery, intracyanine dye was injected into the wound and PDT was performed using a laser diode (810 nm) in two stages: 1) six cycles of 500 mW for 30 sec per cycle in rapid movement; 2) one (case 1) or two cycles (case 2) for 30 sec at 2000 mW. Subsequent examinations showed that the eyelid in both cats had healed, with no evidence of tumour regrowth or ocular irritation [41].

Discussion and Conclusion. The presented historical review of the formation and development of photodynamic therapy shows that this method has come a long way from the first experiments using natural photosensitizers and sunlight to creation of the advanced highly effective drugs and high-precision laser diodes. PDT is used in human and veterinary medicine for treatment of a wide range of oncological diseases, including skin, esophageal, laryngeal, oral cavity, mammary gland cancers, etc. The method demonstrates efficiency both as monotherapy and in combination with other types of treatment, such as chemotherapy, radiation therapy and surgery. Photodynamic diagnostics is also being implemented for precision tumour imaging and therapeutic response monitoring. Innovative approaches based on the use of nanobodies are being developed for targeted delivery of photosensitizers to tumour cells, which increases selectivity and reduces systemic toxicity. PDT proves its potential in treatment of spontaneous tumours in animals, especially in the cases where there are contraindications to traditional treatment methods. The possibility of using PDT as a preoperative treatment to improve tumour resectability and reduce the risk of complications has been demonstrated. Research on optimizing PDT modes and developing new photosensitizers for veterinary use is underway.

However, despite the successes achieved, PDT has certain limitations, such as, for example, relatively shallow penetration of light, possibility of phototoxicity and dependence of this method's efficiency on tissue oxygenation. Therefore, further research should be aimed at:

– development of new generations of photosensitizers with improved pharmacological and photophysical properties;

– optimization of irradiation modes taking into account the absorption spectrum of photosensitizers and the depth of light penetration into tissues;

– studying the molecular mechanisms of PDT action and developing strategies to increase its efficiency by modulating signaling pathways and the immune response;

– development of new methods for delivering photosensitizers to tumour cells;

– conducting clinical trials to assess the efficiency and safety of PDT in deep-seated oncological diseases in humans and animals.

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