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Photodynamic Therapy in Clinical Oncology: What We Need to Know About the Method?

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ABSTRACT

In this review, the authors presented the main aspects of the use of PDT in clinical oncology. Namely, the indications and contra-indications, the leading mechanisms of the antitumor response, adverse reactions and complications are considered in detail, and laser statutes for the conduct of PDT sessions are also presented.

Keywords: photodynamic therapy, photosensitizer, light source, mechanisms

Introduction

Photodynamic therapy (PDT) is an alternative modality for the treatment of malignant tumors. The first steps to use photosensitizing drugs for the cure of skin diseases dates back to ancient India and Egypt, where psoralen-containing plant extracts and light were applied to treat psoriasis and vitiligo [1].

At the end of the 19th century, Oscar Raab, a student of the Faculty of Pharmacology at the University of Munich, carried out experiments on the toxic effects of various substances (quinine, etc.) on Paramaecium caudatum, carrying out scientific research under the supervision of Professor Herman Von Tappeiner. In consequence, in 1903, Tappeiner first introduced the terms «photodynamic», «photodynamic reaction», «photodynamic therapy» [2]. The first data on the successful use of dye eosin and light in the clinic in the treatment of 6 patients with skin cancer, herpes and psoriasis were presented by Dr. A. Jesionek and H. V. Tappeiner. The authors noted the development of complete resorption of foci in 4 patients with a duration of the disease-free period within 1 year [3]. Further development of PDT proceeded along the way of synthesis and creation of new photosensitizers (PS) based on hematoporphyrin, and also the method was tested in patients with malignant tumors.

A significant contribution to the further development of PDT and fluorescent diagnostics was made by the Head of the Center for Photodynamic Therapy of the Institute of Cancer (Buffalo, New-York) T. Dougherty. In 1975, Professor reported a high percentage (50%) of cured laboratory animals with mammary tumors in mice and Walker 256 carcinosarcoma after preliminary administration of photofrin I and its initiation with red light of a xenon lamp after 24 hours. In 1978, an article published in the journal Cancer Research evidenced the successful experience of PDT with photofrin I in the treatment of 113 patients with basal and squamous

Vol. 2, No. 01; 2018

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cell carcinoma, intracutaneous metastases of breast cancer and disseminated melanoma. The incidence of complete regression of tumors was 86.7% [4].

Since then, PDT has gained increasing interest in medical oncology and radiology, representing an experimental tool for the detection and treatment of different nosological forms of tumors located in the skin, lung, esophagus, peritoneum, pleura, genitourinary tract, eye and brain. Intensive clinical research culminated in the approval of PDT for the management of selected malignancies in Europe countries, USA, Canada, Japan, South Korea and China.

According to the definition of professor Geinits A.V., «PDT is a method of local activation of visible red light accumulated in a tumor of PS, which in the presence of tissue oxygen leads to the development of a photochemical reaction that destroys tumor cells» [5]. PDT involves three components: light source, photosensitizing agent (photosensitizer, PS) and tissue oxygen.

Light source

PDT requires a source of light that activates the PS by exposure to low-power visible light at a specific wave length. The therapeutic window for PDT is between 630 and 1200 nm as a light of wavelength, below 630 nm is absorbed by hemoglobin in the tissues and above 1200 nm is absorbed by water. Human tissue transmits red light between 630 nm and 700 nm efficiently, and longer wavelength of the PS results in deeper light penetration. Most photosensitizing agents are activated by red light between 630 nm and 700 nm, penetration depth from 5 mm (λ = 630 nm) to 15 mm (λ = 700 nm) [6].

All sources of radiation that are used in PDT can be conditionally divided into 2 large classes: laser and non-laser. Non-laser sources include light-emitting diodes (λ = 260-1300 nm, output power = 0.1-1 W), fluorescent lamps (λ = 255-1200 nm, output power = 0.05 W), gas-discharge lamps (λ = 300-1500 nm, output power = 0.1-5 W) and metal halide lamps (λ = 250-1000 nm, output power = 0.1-5 W). Their main shortcomings include instability in work, large size and heavy weight, short life and operation (several hundred hours). Laser sources include «solid-state» lasers (λ = 537-670 nm, output power = 2-5 W), copper vapor lasers (λ = 500-700 nm, output power = 5 W), lasers on the vapors of gold (λ = 628 nm, output power = 5 W) and semiconductor lasers (λ = 400-1300 nm, output power = 1-3 W).

Photosensitizing agents

PS is a chemical compound is administered (intravenously or topically) to the patient and gets accumulated into the pathological (tumor) tissues. The tissue is then photoirradiated with light of a specific wavelength. Thousands of natural/synthetic photoactive compounds have photosensitizing potential. They include degradation products of chlorophyll, polyacetylenes, thiopenes, quinines and antraquinones. The majority of the PS used clinically belong to dyes, the porphyrins, chlorins, and furocoumarins. All photosensitizing agents are divided into 3 large classes, namely:

- porphyrin derivatives (Photofrin dihematoporphyrin-ester, Hematoporphyrin derivatives, Tetrasodium-meso-tetraphenylporphyrin, 8-aminolevulinic acid, 5-aminolevulinic acid);

Vol. 2, No. 01; 2018

ISSN: 2581-3366

- chlorophyll-based photosensitizing agents (chlorines: monoaspartyl chlorine e6, chlorine e6, bacteriochlorin a, photolon, radachlorin, photodytazine), purpurins (metallopurpurin, tin etiopurpurin Sn ET2), bacteriochlorins);
- dyes (phthaallocyanines: chloroaluminium tetra-sulfonated Zinc (II) phthalocyanine, naphthalocyanine Aluminium sulfonated phthalocyanine).

Traditionally, porphyrins are referred to the first generation of photosensitizing agents (Photofrin). Photofrin derivatives or synthetically manufactured since the late 1980s are called the second generation (5-Aminolevulinic acid, Temoporfin meta-tetra-hydroxy phenyl chlorin, Talaporfin sodium), biological conjugates of photosensitizers with monoclonal antibodies, nanoparticles or lysosomes - to the third generation.

Ideal PS should be:

- have low light and dark phototoxicity in therapeutic doses;
- have a high selectivity of accumulation in tumor tissue;
- have good luminescence and solubility in aqueous solutions;
- easily removed from the body;
- have a high selectivity of accumulation in malignant tissue and a low level of accumulation in normal tissues;
- have an intense absorption maximum in the region of 660 ± 900 nm;
- have high chemical stability: single, well-characterised compounds, with a known and constant composition;
- have simple and stable formulation;
- have relatively simple production and synthesis, a homogeneous chemical composition.

Despite the fact that an ideal PS has not yet been created, the above criteria are general principles for comparison and further research.

Photodynamic mechanisms

The efficacy of PDT depends on the three following mechanisms:

- direct cytotoxicity;
- vascular damage;
- inflammation and immune host defence.

As a result of photoirradiation, the photochemical reactions begin in the tumor cell. The PS molecule, absorbing a quantum of light, passes from the ground state to the excited state, which is graphically represented in the Yablonsky diagram (Figure 1).

Vol. 2, No. 01; 2018

ISSN: 2581-3366

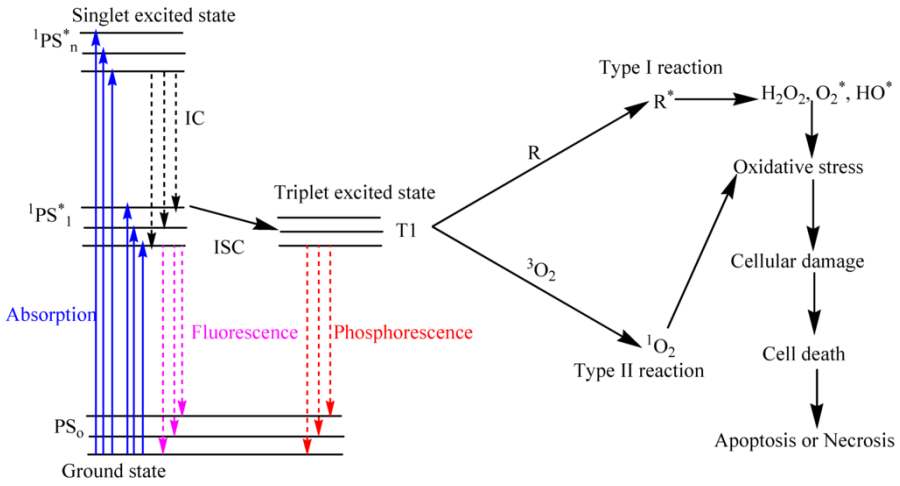

Figure 1. – Jablonski' s energy level diagram for PDT (adapted from C. H. Sibata et al., 2001)

In the future, photochemical reactions of types I and II are initiated. Type I reaction involves electron transfer directly from the PS producing ions or electrons/hydrogen removal from a substrate molecule to form free radicals. These radicals react rapidly with oxygen, resulting in the production of highly reactive oxygen species (superoxide, hydroxyl radicals, NO-radicals and hydrogen peroxide). Type II photo-oxidation reaction produce the electronically excited and highly reactive state of oxygen (singlet oxygen). Possessing a high oxidation potential, ROS interact with the lipids of the membranes of organelles of the tumor cell with the formation of oxidation products, destabilization and subsequent destruction of the cell as a whole.

One of the leading roles in tumor damage in PDT is played by a vascular component. Henderson B.D. et al. proposed in 1985 the assumption of the leading role of blood vessel damage in the realization of the photodynamic effect. The result of photoirradiation is a violation of the integrity of the endothelium of the blood vessels, the subsequent activation and aggregation of platelets with the release of thromboxane, the formation of parietal or occlusive thrombi, emergence of an intestinal edema, leading to vasoconstriction, vasodilation and vascular stasis. The consequence of all of the above is a complete cessation of blood flow in the tumor and its death due to developing ischemic necrosis [7].

The third mechanism of tumor damage with PDT, which is indirect in nature, is the immune system response in response to photoirradiation. In response to photodynamic action, the tumor antigen is captured by dendritic cells through phagocytosis of apoptotic cells, capture of necrotic cell fragments, or presentation of the antigen in combination with the extracellular heat shock protein HSP70. This protein forms strong and stable complexes with tumor cell cytoplasm antigens and binds to the receptors of dendritic cells, which leads to their activation and maturation. Mature dendritic cells migrate to the lymph nodes where they present tumor antigens in complex with class I and II molecules to T lymphocytes: cytotoxic CD8+ and CD4+ helper cells. The activation of T-lymphocytes requires the release of cytokines, which play a significant role in determining the type of immune response that develops after antigen presentation [8].

Vol. 2, No. 01; 2018

ISSN: 2581-3366

Next T-helpers differentiate into Th1, Th2 and a number of other subclasses [9]. Th1 cells by secretion of IL-2, interferon γ and tumor necrosis factor determine the development of an immune response that includes the activity of CD8 + T-lymphocytes, macrophages and natural killers. Th2 cells through the secretion of IL-4, IL-5, IL-6, IL-10, IL-13 are responsible for the humoral immune response. Other subclasses of T-lymphocytes (Th3, Tr1) secrete IL-10 and tumor growth factor β, responsible for the strength of the immune response. Activated CD4 + and CD8 + T-lymphocytes migrate from the lymph nodes to the tumor. CD8 + cells directly destroy tumor cells, CD4 + act indirectly through other cells of the immune system (macrophages) [11].

The result of all the above reactions occurring in the tumor cell are apoptosis, autophagy and necrosis. The main factor determining the path of death of a tumor cell is the integrity of the cell membrane. In the presence of defects of this structure, necrosis is paramount, in the absence of apoptosis [7].

Indications of PDT

Three most important directions of the clinical application of PDT are generally accepted, namely,

- use of a radical program designed for complete cure (in the early stages of malignant tumors as an alternative to radiation and surgical methods of treatment);
- with a high risk of exposure during the operation or the impossibility of its implementation for other reasons;
- use as a component of combined and complex treatment (in combination with radiation therapy and chemotherapy) in the prevalent forms and recurrences of malignant tumors;
- use with a palliative purpose for the recanalization of hollow and tubular organs, as well as for far-reaching processes, tumor stenoses;
- with some metastatic forms of tumors in order to improve survival and quality of life of patients.

Summarizing the main world experience of the use of PDT in oncology, we came to the conclusion that this method of treatment has proved itself in the treatment of many nosological forms of tumors, namely:

1. Skin cancer:

1.1 basal, squamous and metatype skin cancer T1-4N0M0;

1.2 primary, recurrent and residual tumors;

1.3 tumors of anatomically uncomfortable localization (auricle, angle of the eye, tip of the nose);

1.4 tumors resistant to traditional methods of treatment;

1.5 locally distributed tumors, when the size of the tumor node may be 10 or more cm in diameter at a depth of tumor infiltration up to 1 cm;

1.6 patient's refusal from surgery, radiation and chemotherapy;

1.7 multiple and extensive tumor lesions.

2. Intradermal and subcutaneous metastases of melanoma and breast cancer.

3. Pre-tumor diseases of the cervix and vulva (cervical intraepithelial dysplasia, leukoplakia), minimally invasive forms of cervical cancer.

Vol. 2, No. 01; 2018

ISSN: 2581-3366

4. Cancer of the oral mucosa, tongue and lower lip:
4.1 squamous cell carcinoma T1-2N0M0;
4.2 high risk of complications after radiation, surgical treatment in elderly and somatically burdened patients;
4.3 tumors resistant to standard methods of treatment;
4.4 the patient's refusal from traditional methods of treatment.
5. Primary and recurrence malignant brain tumors:
5.1 multiform glioblastoma Grade IV, primary and recurrent form;
5.2 anaplastic and fibrillar astrocytoma, Grade II-III, primary and recurrent form;
5.3 adenoma;
5.4 metastatic brain tumors.
6. Lung cancer:
6.1 central lung cancer, T1-2N0M0 with localization in the trachea; main, intermediate and lobar bronchi (exophytic and endophytic form up to circular lesion, the presence of atelectasis are not contraindications);
6.2 high risk of surgical complications after radiation, surgical treatment in elderly and somatically burdened patients with central lung cancer;
6.3 the patient's refusal of traditional methods of treatment.
7. Esophageal carcinoma:
7.1 primary cancer T1N0M0 in the presence of contraindications to surgical and/or combined treatment;
7.2 early relapse after radiation therapy;
7.3 palliative PDT for the purpose of recanalization in obturating tumors;
7.4 the patient's refusal from traditional methods of treatment.
8. Stomach cancer:
8.1 primary cancer T1N0M0 of any histological structure, mucous or mucosal-submucosal growth;
8.2 early relapse in anastomosis;
8.3 palliative PDT in stenosing cancers of the cardiac part of the stomach (permissible - with passage to the esophagus) for the purpose of recanalization;
8.4 patient's refusal from traditional methods of treatment.
9. Mesothelioma of the pleura.
10. Locally-distributed recurrent prostate cancer.
11. Superficial bladder cancer:
11.1 superficial-steled cell carcinoma of the bladder; primary, recurrent form;
11.2 exophytic bladder cancer Tis-1N0M0 with localization in the region of the bottom, lateral walls, multiple lesions are permissible, regardless of previous treatment;
11.3 ineffectiveness of traditional methods of treatment;
11.4 indications for cystectomy.
12. Pancreatic cancer.
13. Mammary cancer:
13.1 Paget cancer T1-2N0M0;

Vol. 2, No. 01; 2018

ISSN: 2581-3366

13.2 recurrence of breast cancer on the chest wall after surgical treatment;
13.3 intradermal metastases after surgical, combined and complex treatment (simultaneous radiotherapy and chemotherapy are not contraindications to PDT);
13.4 primary breast cancer T1-2N0M0 (nodular form) with a categorical refusal of the patient from surgical treatment and the presence of severe co-morbidities.

With a detailed analysis of available literature data, it can be concluded that PS of different classes have been well recommended in PDT of various malignant tumors. Thus, hematoporphyrin and its derivatives (photophryn I/II, photohem, λ = 630 nm): skin cancer, malignant gliomas, cancer of the stomach, esophagus, lungs, bladder, cervical dysplasia; 5-ALA and its derivatives (λ = 635 nm): skin cancer, actinic keratosis; foscan (λ = 652 nm): scalp and neck cancer, breast, pancreas, stomach and intestinal cancer; sulfonated aluminum phthalocyanine (photosens, hexasense, etc., λ = 670 nm): skin cancer, breast, lung and digestive tract cancers; mono-aspartyl-chlorin e6 (taloporfin, λ = 660 nm): lung, rectum and prostate cancers, malignant gliomas; photolon (λ = 661±5 nm): skin cancer, intradermal metastases of melanoma and breast cancer, lung cancer, precancerous diseases of the cervix and vulva, mucous membranes, malignant gliomas; texaphyrins (lutrin, optrin, antrin, etc., λ = 732 nm): prostate and cervix cancers, malignant gliomas [7].

The results of the studies demonstrated above confirm a wide range of PDT use, which is possible due to the availability of this method a number of advantageous advantages in comparison with existing standard methods of treatment. The main ones are:

1. minimal toxicity to the surrounding normal tissues, due to the selective accumulation of the PS in the tumor;
2. minimal risk of developing severe pain syndrome;
3. minor systemic effects;
4. lack of mechanisms for primary and acquired resistance;
5. the possibility of an outpatient procedure;
6. the possibility of combination with other methods of treatment;
7. absence of limiting cumulative doses of PS and light exposure, the possibility of repeated repetition of the procedure;
8. ease of use for the multiple nature of the lesion;
9. good cosmetic results;
10. the possibility of implementing organ-preserving methods of treatment.

PDT can not be called a «panacea» for cancer, since the method has its drawbacks, which can be attributed to the following:

1. limited depth of penetration of laser radiation into the tumor (from 2 to 15 mm depending on the wavelength);
2. dependence of the effectiveness of the procedure on the nature of the blood supply and the degree of tumor oxygenation;
3. lack of morphological control after treatment;
4. high cost of some photosensitizing agents;
5. empirical nature of the selection of exposure regimes.

Vol. 2, No. 01; 2018

ISSN: 2581-3366

Contraindications of PDT

According to a number of authors [7], contraindications for the use of PDT in the treatment of cancer patients are minimal and are of an individual nature. Any of them is exposed after assessing the overall status of the patient, the extent of the disease and the patient's desire to receive treatment with this method. Gamayunov S.V. et al. concluded that the main contraindications for PDT are:

1. cardiovascular and respiratory insufficiency;
2. liver and kidney disease in the stage of decompensation;
3. systemic lupus erythematosus
4. cachexia;
5. individual intolerance of the drug to absolute contraindications
6. allergic diseases [11].

Complications and adverse reactions of PDT

The main side effect of photoradiation is skin phototoxicity, the duration of which is directly related to the half-life of the PS from the patient's body. Depending on the class of photosensitizing agents, this indicator varies from 2-3 days to several months. So, this indicator for a chlorine-based PS (photolon, photoditazine, chlorine e6) is about 24-72 hours, 2 weeks (foscan), 48-96 hours (porphyrins and their derivatives) and 1-3 months (dyes: photosens, phthalocyanine derivatives). The main preventive measure aimed at minimizing the main symptoms of skin phototoxicity (itching, hyperthermia, conjunctivitis, dermatitis) is strict adherence to the light regime.

PDT sessions, as a rule, are accompanied by the emergence of a pain syndrome of varying severity: from burning sensation and tingling to severe pain in the photo-irradiation zone, which is of a permanent nature with possible irradiation along the course of neural bundles. The intensity of pain depends on the area of exposure and persists for 1-5 days after the treatment. For the prevention of pain syndrome, narcotic and non-narcotic analgesics are used.

In a number of patients, general weakness may appear, increase in body temperature to + 37-37.5° C, development of catarrhal symptoms that are temporary.

Goldman M.P. et al. systematized the main adverse reactions that occur with PDT with 5-ALA (levulan, metvix) for malignant and benign tumors, as well as non-tumor diseases. The main side reactions observed by the authors, apart from the pain syndrome, were temporary hyperpigmentation, followed by residual erythema (2%), irreversible alopecia – for basal cell skin cancer; erythema, edema and detachment of the epidermis, erosion, ulcers – for cutaneous manifestations of T-cell lymphoma; short-term decrease in sensitivity, swelling, skin peeling (disappears after 1-2 weeks), damage to the sebaceous glands, leading to dry skin, development of infections (rarely) – for precancerous skin diseases (actinic keratosis); nausea, erythema, acne scars – for acne [11].

All the complications and adverse reactions that occur with PDT in the vast majority of cases are temporary, easy to stop, do not increase the duration of treatment and, as a rule, do not affect cosmetic effects.

Vol. 2, No. 01; 2018

ISSN: 2581-3366

Conclusion

PDT is an alternative method of treating malignant and premalignant diseases. Despite the fact that the history of PDT is about 120 years old, at the moment the place of PDT in modern clinical oncology is beyond doubt. PDT has gained increasing interest in medical oncology and radiology, representing an experimental tool for the detection and treatment of different nosological forms of tumors located in the skin, lung, esophagus, peritoneum, pleura, genitourinary tract, eye and brain. Intensive clinical research culminated in the approval of PDT for the management of selected malignancies in Europe countries, USA, Canada, Japan, South Korea and China. In the leading clinics and scientific centers of the world, this area is actively used and included in the scheme of combined and complex treatment, and in some cases is used as an independent method.

In our opinion, PDT can be considered as a safe, well tolerated and highly effective option in the treatment of malignant and premalignant diseases.

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