REVIEWS OF LITERATURE

PHOTODYNAMIC THERAPY IN THE CLINICAL PRACTICE

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Abstract

The review is on opportunities and possibilities of application of photodynamic therapy in clinical practice. The advantages of this method are the targeting of effect on tumor foci and high efficiency along with low systemic toxicity. The results of the set of recent Russian and foreign clinical trials are represented in the review. The method is successfully used in clinical practice with both radical (for early vulvar, cervical cancer and pre-cancer, central early lung cancer, esophageal and gastric cancer, bladder cancer and other types of malignant tumors), and palliative care (including tumor pleuritis, gastrointestinal tumors and others). Photodynamic therapy delivers results which are not available for other methods of cancer therapy. Thus, photodynamic therapy allows to avoid gross scars (that is very important, for example, in gynecology for treatment of patients of reproductive age with cervical and vulvar cancer), delivers good cosmetic effect for skin tumors, allows minimal trauma for intact tissue surrounding tumor. Photodynamic therapy is also used in other fields of medicine, such as otorhinolaryngology, dermatology, ophthalmology, orthopaedics, for treatment of papilloma virus infection and purulent wounds as antibacterial therapy.

Keywords: photodynamic therapy, photosens, alasens, fotoditazin, radachlorine, antibacterial photodynamic therapy, vulvar cancer, cervical cancer, lung cancer, esophageal cancer, gastric cancer, skin cancer.

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Currently, the new therapies based on advances in photochemistry, photobiology, and quantum physics become all the more common in clinical practice. The laser medicine progress has led to a fundamentally new technology used in the treatment of various diseases, i.e. photodynamic therapy (PDT) [1-3].

Photodynamic therapy is a method featuring a high efficiency and having almost no side effect or complication. It is based on the ability of certain drugs, i.e. photosensitizers, to accumulate selectively and remain in the tissues of malignant tumors, highly proliferative tissues and a number of microorganisms. Under the influence of the laser energy in the sensitized cells and tissues, a photochemical reaction is develop with the release of singlet oxygen and free radicals, which leads to loss of life and destruction of sensitized substances not affecting the healthy tissues and organs. Healing occurs as a natural repair process, so the method is the most organ-preserving and well-tolerated, allowing to repeat the treatment several times, if required [4, 5].

In the last decade, due to the emergence of domestic photosensitizers and lasers for PDT, a growing number of researchers explores the possibilities of this method in various fields of medicine.

PDT in purulent surgery

Attempts of PDT with the aim of antibiotic treatment have been undertaken yet in the early 20th century. However, the limited knowledge about the mechanisms of action, limited possibilities of synthesis of effective photosensitizers for lethal bacteria photosensitivity and the lack of the required light sources suspended the research for many years.

Currently, the antimicrobial PDT uses the experience accumulated during PDT of tumors. The local distribution of the photosensitizer, the local light exposure, the use of fiber optics and endoscopic techniques allow obtaining a good clinical effect. Several authors have shown that the majority of Gram-negative and Gram-positive bacteria may be photoinactivated successfully using the water-soluble phthalocyanines [6].

The data from other authors have shown good clinical effect and the absence of HPV in tissue specimens after photodynamic therapy [7].

In recent years, scientific publications on the use of photodynamic therapy for the treatment of festering wounds appeared, which marked the advantages of PDT compared to the conventional therapy, in particular a pronounced anti-bacterial and anti-inflammatory effect. The pathogens do not develop resistance to PDT, which is important in the treatment of chronic infectious processes. Bactericidal effect of PDT when applied topically is determined by the area of laser irradiation of sensitized tissues, thus avoiding systemic side effects observed with the use of antibiotics and antiseptics. Recently, the photodynamic therapy of purulent wounds is carried out using chlorine series and has a positive effect on the course of wound healing manifested by strong antibacterial effect, accelerated cleansing of wounds from purulent necrotic detritus and acceleration of the wound defect healing [8].

In the clinical study, A.V. Heinz et al. report the results of treatment of 120 patients with purulent and long-term healing soft tissue injuries of different etiology and location using Photodithazine photosensitizer (BETA-GRAND LLC, Russia, registration certificate No. LS 001246 dated May 18, 2012) in the form of a gel. It was concluded that this treatment helps to accelerate the clearance of wounds from purulent necrotic detritus, the appearance of granulation, acceleration of epithelialization 1,5-2 times and reduction of the time of complete healing of purulent wounds by 5-7 days compared to conventional treatment [7].

It should be noted that the developed PDT method for purulent wounds using chlorine series photosensitizers is highly effective, pathogenetically justified, providing for acceleration of granulation and complete healing of purulent wounds. This is especially important in the treatment of frail elderly patients with a reduced rate of reparative processes and the possibilities of immune response.

The PDT effectiveness is not dependent on the sensitivity of the spectrum of pathogens to antibiotics and it has a detrimental effect on the antibiotic-resistant strains of Staphylococcus aureus, Pseudomonas aeruginosa and other bacteria. The development of microbial resistance to PDT is unlikely, since the photodynamic damage is due to the cytotoxic effect of the singlet oxygen and free rad-

icals. It should also be noted that during the long-term treatment of infectious processes, the local antimicrobial effect of PDT is not weakening, and the bactericidal effect is local and has no systemic detrimental effect on saprophytic flora of the body.

PDT in endocrinology

In endocrinology practice, the pathologic processes accompanied by formation of skin ulcers are quite common. Ulcer formation is an indication of the disease morbidity, causes considerable difficulties in treatment, and requires prescription of systemic and topical medicines. In recent years, there appeared a number of papers on the use of PDT with Photodithazine as a photosensitizer in the treatment of venous ulcers being a complication of diabetes. At the same time, a major factor of PDT therapeutic effect is its bactericidal and bacteriostatic effect. The results of treatment of 72 patients with trophic ulcers who underwent PDT with photodithazine in the form of a gel, both in stand-alone options, or in combination with NO-plasma treatment, were analyzed. It was concluded that PDT helps to accelerate the wound cleansing from devitalized tissues, normalizes the microcirculation disorders, enhances the phagocytosis, stimulates the fibroblast proliferation and maturation of the granulation tissue, as well as promotes the ulcer epithelialization on day 12-15 [9].

PDT in orthopedics

Arthrosis and arthritis in the elderly is a challenge of modern medicine. Due to age and presence of co-morbidities, radical treatment in the form of joint replacement is often not possible or associated with a high risk of perioperative complications. In recent years, there have been publications on the use of PDT with arthroscopy for treatment of arthritis and other inflammatory processes in the large human joints. In inflammatory processes in the large human joints, PDT allows stimulating the local and general blood circulation, helps to relieve swelling, inflammation and pain syndromes, and to develop the joint movement. The results of treatment of 11 patients with deforming arthrosis, synovitis and bursitis who underwent PDT with photodithazine were published. The drug was administered intravenously at 0,05 mg/kg of the patient's body weight. After PDT, the intensity of pain syndrome and swelling in the lesion projection decreased, as well as the local temperature reaction of the skin was normalized [10]. Another study analyzed the results of treatment of 86 patients 4 to 17 years old with a clinical diagnosis of rheumatoid arthritis, who underwent PDT with photodithazine in the form of a gel. The use of this non-invasive method allowed stopping the main clinical signs of inflammation in the joints effectively. There was a marked improvement according to X-ray and ultrasound studies in the form of reduction of effusion in the joint cavity [11]. Thus, it was concluded that PDT is highly effective in the treatment of inflammatory diseases of the joints.

PDT in ophthalmology

Currently, the age-related macular degeneration is a leader among the factors of blindness and low vision development in patients after 65 years old. At the heart of development of the exudative age-related macular degeneration there are newly formed vessels, i.e. subretinal neovascular membrane, which leads to destruction of the neuroepithelium and irreversible loss of vision. In modern literature, the concept of a single treatment of subretinal neovascular membrane does not exist. On the basis of experimental studies in many countries, a clinical trial to study the PDT effectiveness in the treatment of neovascularization was launched successfully.

The results of the Russian research on the effectiveness of PDT treatment with photosens (FSUE «SSC «NIOPIK», Russia), registration certificate PN000199/02 dated March 04, 2010) as a single agent and a combination of PDT with anti-VEGF in 38 patients with age-related macular degeneration were published.

After treatment, patients have improved their visual acuity, as well as showed a decrease in activity of the subretinal neovascular membrane, which is confirmed by the results of the angiographic pattern of the fundus and average retinal thickness in the foveola [12].

Thus, the data show the effectiveness of PDT with photosens in patients with subretinal neovascular membrane against the background of age-related macular degeneration.

PDT in otorhinolaryngology

In recent years, scientific publications on the use of photodynamic therapy in otorhinolaryngology in order to increase the effectiveness of treatment of patients with purulent-inflammatory diseases of the ear, nose and throat in the background of the decreased immunity and increased resistance to antibiotics. The PDT results in the treatment of purulent sinusitis in 41 patients with radachlorin photosensitizer were published (RADA-PHARMA LLC, Russia, registration certificate No. LS-001868 dated December 16, 2011). The PDT effectiveness for purulent sinusitis was evaluated in the clinical course of the disease, and according to repeated microbiological studies of the sinus washings. The analysis of treatment results showed a high efficiency. 38 patients had a complete recovery (absence of clinical signs and negative results of bacteriological control); 3 patients, according to bacteriological study, showed a significant decrease in specific pathogen titers in the absence of clinical signs of the disease [13].

The evidence from several studies suggest that the use of PDT in simple forms of chronic tonsillitis also allows achieving a complete cure of the disease, and to achieve stable remission of the toxic-allergic form. In one study, PDT with topical application of radachlorin in 50 patients with various forms of chronic tonsillitis has led to the treatment acceleration, reduction or disappearance of the local symptoms of the disease, improvement of general condition, and absence of quinsy during the two-year follow-up period [14].

PDT in the treatment of human papillomavirus infection

The problem of respiratory papillomatosis has been attracting the attention of researchers for years. Laryngeal papilloma is a benign tumor, but it is prone to rapid growth and frequent recurrence upon localization at the narrowest point of the breathing tube. To date, there is no causal treatment of this disease. The combined approaches to the treatment of respiratory papillomatosis, combining the surgical and conservative treatment, were developed. However, they have not solved the main problem of this disease, namely the frequent recurrence. In addition, because of the frequent recurrence of the disease, many operations lead to scarring in the larynx and trachea, and violation of their functions. In the last decade, the photodynamic therapy is actively used both abroad and in our country as an alternative method for treatment of this disease. Thus, A.N. Nasedkin et al. report the results of treatment of 19 patients diagnosed with respiratory papillomatosis by PDT with radachlorin. 4-6 weeks after PDT, all patients showed a therapeutic effect, and the complete eradication of HPV infection in 77% cases. The authors note that the appearance of scars in the larynx and trachea, or aggravation of the existing scarring process has been recorded after treatment [15].

Currently, the main role in the pathogenesis of pretumor and neoplastic cervical pathology development is played by the highly oncogenic human papillomavirus (HPV), namely type 16, 18, 31, 33, 45 and 52. In recent years, scientific publications on the prevention and treatment of HPV-associated pretumor and tumor cervical pathology by PDT appeared. So, O.I. Trushina et al. report the results of treatment of 104 patients with a diagnosis of dysplasia of the 2nd or 3rd degree and in situ carcinoma of the cervix, associated by the highly oncogenic HPV genotypes with photohem. After PDT, a complete eradication of HPV DNA was achieved in 94% of cases, and a partial eradication of HPV was diagnosed in 6% cases, which shows a pronounced antiviral effect of the treatment [16].

PDT for primary and recurrent skin cancer

In the last decade, a steady increase in the incidence of epithelial malignant skin tumors has been observed all over the world. In the structure of cancer incidence, the malignant skin tumors rank second. The annual growth rate of the patients with disease is 3% to 10%. The basal cell skin cancer (BCC) represents a large proportion of malignant tumors of the skin; it accounts for 75% to 90% in the overall structure of malignant tumors of the skin [17].

The problem of BCC treatment is relevant for our population. This is due to the high morbidity, recurrent nature, frequent localization on exposed skin, especially on the face, the lack of effectiveness of existing therapies, and significant cosmetic defects. The major treatment

methods for epithelial malignant skin tumors include the surgical technique, radiation therapy, cryosurgery, and diathermocoagulation. However, these treatment methods have several disadvantages, i.e. significant side effects, limitations when the re-treatment is required, and not always effective enough and organ-preserving treatment outcomes.

Currently, one of the most effective, minimally invasive and organ-preserving treatment of epithelial malignant skin tumors is photodynamic therapy.

The interest of dermatology and oncology specialists in PDT is determined by the fact that the destruction of a tumor or pathological tissue is achieved upon irradiation with laser light after topical or systemic administration of the photosensitizer, which eliminates the risk of uncontrolled thermal damage to the tissues and organs, i.e. the photodynamic damage effectively destroys the tumor and pathological tissue, while preserving the surrounding healthy tissues as much as possible [18].

In recent years, there have been numerous publications in foreign and domestic literature on the results of successful use of PDT in the treatment of skin cancer with derivatives of 5-aminolevulinic acid [19-22]. A positive effect in the treatment of skin cancer by PDT ranges from 70 to 100%, depending on the tumor stage and location, photosensitizer chemical structure or dose, as well as the laser irradiation parameters. A complete tumor regression is registered in 75-80% of patients, and the duration of recurrence-free period ranges from 2 months to 5 years [23, 24].

Thus, PDT significantly expands the arsenal of modern methods for treatment of skin cancer. The method is successfully used in the awkward location of the tumor (pinna, eye corner, eyelids, nose) with good cosmetic results. The use of the photodynamic therapy is indicated for tumors resistant to the previous methods of conventional therapy.

Along with primary and recurrent malignant tumors, a special place is occupied by metastatic lesion of the skin. According to the literature, the frequency of cancer metastasis from internal organs into the skin ranges from 0,29 to 3.3% [25]. The breast cancer is the largest group of metastatic malignant skin tumors. Metastases are commonly located on the chest wall in the vicinity of the primary tumor, and mainly develop after surgery. The major method for treatment of patients with intradermal metastatic breast cancer is chemotherapy or hormone therapy with multiple repetition of treatments. The second most common cause of skin metastases after breast cancer is melanoma. Cutaneous and subcutaneous metastases occur in approximately 2-10% of cases. Metastases can be single or multiple, located near the primary tumor, or remotely from it. The metastatic intradermal melanoma can be treated by surgery, radiation therapy, or combination therapy. However, with the appearance of new foci of disease in the skin, their use becomes questionable.

The growth of metastases in the background of ineffectiveness of conventional treatment methods worsens the life forecast of the patients, contributes to the appearance of pain, edema, intoxication, which affects the general and psycho-emotional state of patients and reduce their quality of life.

Such patients need to be treated by alternative methods with high antitumor efficacy. One of these methods is PDT. Group of authors performed PDT using the domestic photosensitizers in 36 patients with intradermal metastases. The prolonged use of PDT in patients with intradermal metastatic breast cancer and melanoma allowed obtaining a complete tumor regression in 39.3% and 38% respectively, and partial tumor regression in 46% to 52,4%. All patients had tumor resistance to conventional treatment in the background of the previously conducted conventional therapy [26].

Kaposi's sarcoma is a rare angioproliferative disease associated with human herpesvirus of type 8. Despite the increase in the frequency of idiopathic type of Kaposi's sarcoma in recent years, its radical treatment method has not been developed, and the treatment is largely palliative, providing a temporary effect. A promising method for treatment of Kaposi's sarcoma is PDT. The results of treatment of 15 patients with intratumoral administration of domestic photosensitizers were published. Against PDT, the clinical benefit in the form of improvement of the general condition of patients and reduced area of the tumor lesion was observed, which in turn leads to improved quality of life [4].

Thus, PDT largely affects the quality of life of this difficult group of patients.

PDT for early central lung cancer

In recent decades, lung cancer steadily occupies the first place in the structure of morbidity and mortality from cancer. Empowering of endoscopic diagnosis of early forms of cancer of the trachea and the large bronchi stimulated the development of a new direction in the endoscopic treatment, i.e. radical or conventionally radical endoluminal surgery with removal of the primary malignant tumor, affecting the bronchial mucosa only. The standard type of treatment for early central lung cancer is surgery.

However, about 20-50% of patients are functionally inoperable. They are subjected to radiotherapy or not treated at all. The most promising direction in the treatment of patients with lung cancer is photodynamic therapy, which can be used in combination with conventional methods [27]. In recent years, the clinical experience of functional-sparing and organ-preserving treatment methods for this disease using PDT was accumulated.

According to Y. Hayata et al., PDT's efficiency for early central lung cancer (CLC) depends on the growing shape and size of the primary bronchus cancer. Thus, for a superficial type of tumors (up to 5 mm), a complete regression with PDT is achieved in 91% cases, and for tumors 5 to 10 mm – in 89,4% cases. The nodular and polypoid tumor types with diameters up to 5 mm, a complete regression was noted in 93.7% cases, while for tumors 5 to 10 mm – in 62,0% cases [28]. P.N. Mathur et al. after photodynamic therapy in 99 patients with early CLC at IA degree with the tumor up to 1 cm in diameter, a complete regression was observed in 95% patients, and with the tumor size of 2 cm or more in 46% cases. The best PDT result was observed with the tumor size up to 1 cm when the distal border of the tumor was clearly visible at bronchoscopy. In this case, a complete regression in 98% cases was achieved. The tumor relapse was diagnosed in 13% patients [29]. According to PDT in 517 patients, presented by researchers from the UK [30], a 5-year survival with complete tumor regression was 70%. For PDT (23 tumors) at the Mayo Clinic (USA), a complete tumor regression was achieved in 69.5% of cases. During follow-up, 24% of patients in this group showed a new focus of the metachronous lung cancer [31].

There is evidence of domestic researchers about the PDT results for early CLC in 37 patients with local photosensitizers (photohem, radachlorin, photosens). As a result of treatment, a complete tumor regression was obtained in 87% patients [32].

According to many domestic and foreign authors, PDT for the CLC is a highly effective method. The method has no real counterparts, especially in patients with primary bronchi multiple lesions, and high risk of surgery complications. The use of this method allows to improve the results of organ-preserving treatment of cancer patients [32, 33].

PDT in the treatment of stenotic malignant tumors of the respiratory tract

Pulmonary atelectasis and pneumonia caused by occlusion of the bronchus lumen impair the quality of the patients' life and delay the commencement of the specialized treatment in most patients. The photodynamic therapy is an alternative treatment for palliative care of inoperable patients. The literature contains information about PDT with domestic photosensitizers in 55 patients with stenotic malignant lung tumors in the central location. After treatment, this group of patients had a clinical benefit in the form of reduced tumor stenosis of the bronchi with varying degrees of severity, which in turn leads to improved quality of life [34].

PDT for primary and metastatic pleural lesion

Accumulation of fluid in pleural cavity is a frequent clinical manifestation of malignant pleural lesions and is commonly diagnosed with many tumor locations. The systemic combination chemotherapy is used for treatment of metastatic pleurisy; the intrapleural non-specific anti-cancer drugs are administered. The fluid accumulation in the pleural cavity stops after systemic chemotherapy in 30-60% cases only, on the average. In recent years, a prolonged intrapleural PDT with photosens has been applied for treatment of pleurisy in primary tumor and metastatic pleura. Laser irradiation of the pleural cavity is performed through the cylindrical diffusers installed for the whole period of treatment to the areas with the largest tumor lesion. According to several authors, the pro-

longed intrapleural PDT in patients with mesothelioma and metastatic pleura allows achieving a stable termination intrapleural exudation in 92% patients during 3,5 years of follow-up [35].

Thus, the prolonged intrapleural PDT of malignant pleurisy allows achieving the good long-term effect and may be the method of choice for treatment of malignant pleurisy. Intrapleural PDT creates favorable conditions (cessation of fluid accumulation in the pleural cavity) for further cancer treatment and for improvement of the quality of life of this large group of patients for a long period.

PDT for early cancer of the esophagus and stomach

Morbidity and mortality from cancer of the esophagus and the stomach has been growing steadily over the past decade. In Russia, more than 40 thousand gastric cancer patients and about 8 thousand esophageal cancer patients are diagnosed annually. The recent improvement of endoscopic and ultrasound diagnostics methods can significantly improve the quality and frequency of detection of precancerous diseases and early forms of esophageal and gastric cancer.

Currently, according to the world literature, a considerable experience related to the use of PDT in the treatment of early cancer of esophagus and stomach has been accumulated. An important advantage of this method is that it can be used repeatedly for a multi-cycle treatment with an interval of 1-3 months. Upon reaching of clinical signs of tumor stabilization, the multi-cycle PDT can be conducted for many years.

In the work of domestic authors, PDT was performed in 116 patients (121 tumor lesions) with the initial cancer of the esophagus and stomach using the intravenous domestic photosensitizers. A complete regression of 90 (74.4%) foci and a partial regression of 31 (25,6%) tumor foci were obtained [36].

To date, one of the most urgent problems of modern gastroenterology and oncology is the treatment of Barrett's esophagus. In the presence of a severe dysplasia and a genetically determined risk of adenocarcinoma development, the method of choice is the subtotal resection of esophagus. However, this position is not shared by the majority of clinics in the world, and the preference is given to the organ-preserving treatments. The conservative ablation of lesions primarily by PDT is well-grounded [37].

Thus, PDT is a promising method, allowing to achieve goods results in the treatment of early forms of the cancer of esophagus and stomach, and can be an alternative to the surgical treatment of patients with severe comorbidities.

PDT in the treatment of stenotic cancer of esophagus and cardia

The severity of condition of the cancer patients, and poor quality of life is often caused by a tumor lesion of the digestive tract. In recent decades, esophageal cancer is responsible for the highest mortality rate in Russia. Dysphagia for esophageal cancer significantly impairs the patient's condition and quality of life. One of the alternative methods of providing a palliative care for inoperable patients with stenosing cancer of the upper gastrointestinal tract is PDT. The results of endoscopic PDT with domestic photosensitizers in 147 patients are published. Upon relapse of dysphagia after stenting due to the tumor germination through the prosthesis wall, or tumor growth above or below the stent, PDT is the only possible way to eliminate the tumor stricture. Palliative PDT is also shown for cancer recurrence upon esophagogastric anastomosis after proximal gastrectomy, with a high prevalence of recurrent process about the esophagus. Recanalization effect lasts for 3 months on the average. Upon dysphagia relapse, the repeated PDT also has a beneficial effect. It is expedient to conduct a multicycle PDT to achieve the highest quality of life for this group of patients [38, 39].

Thus, in comparison with the other methods of palliative care for incurable patients with stenotic esophageal and gastric cancer, endoscopic PDT is the best option of integrated treatment. A significant increase in survival rates and quality of life was obtained.

PDT in metastatic lesions of the peritoneum

Gastric cancer remains one of the most common malignant tumors and is the second largest in the structure of cancer-related deaths. In 70% patients, at the time of

diagnosis the tumor process is locally advanced or generalized, which determines an extremely high mortality in the first year after diagnosis. A high level of surgical techniques, development of combined and expanded surgeries subject to the maximum compliance with the principles of cancer does not exclude the development of peritoneal dissemination, the major option of the gastric cancer progression. Given the nature of the mechanisms of peritoneal dissemination development, the new methods of specialized therapeutic impact on the area of the surgical field and peritoneum are sought to reduce the risk of peritoneal carcinomatosis, raising the level of ablation and antiablation and increase of the disease-free period in the locally advanced and metastatic gastric cancer. One such method is intraoperative PDT. The literature suggests a sufficient efficacy and safety of intraoperative PDT with domestic photosensitizers in patients with peritoneal dissemination upon metastatic gastric cancer in combination with palliative surgery to increase the duration of the delaying time to relapse and the overall survival in this group of patients [39, 40].

PDT for superficial bladder cancer

In the structure of cancer incidence, the bladder cancer ranks 8th among men and 18th among women, accounting for 70% of all malignant tumors of the genitourinary system. Currently, there is a tendency to an increase in the incidence of this pathology. The major treatment for early bladder cancer is surgery, namely the transurethral resection within healthy tissue to the muscle layer. However, this does not allow reducing the rate of relapse, which is 40-90% during the first year of follow-up [41]. Given the dissatisfaction with the treatment outcome, the search for more effective ways and means of influencing the tumor and the bladder mucosa to prevent the disease relapse and progression continues.

Over the past ten years, the literature has been increasingly discussing the results of clinical studies based on physical effects, as well as a combination of this kind of influences with conventional treatment methods for prevention of recurrence of the superficial bladder cancer. To date, one of the most promising areas is considered to be a PDT.

According to A.P. Berger et al., when using PDT with 5-aminolevulinic acid as an adjuvant therapy, the disease-free survival rate was more than 2,3 years in every second patient [42].

In recent years, there have been publications on the use of photodynamic therapy combined with intravesical chemotherapy in patients with non-muscle-invasive bladder cancer as an adjuvant treatment. A.Y. Zubkov et al. report the surgical treatment (transurethral resection of the bladder), followed by an adjuvant PDT with domestic photosensitizers and an intravesical chemotherapy in 35 patients with non-muscle-invasive bladder cancer. During the follow-up period of 6 to 24 months, no progression or symptom of tumor recurrence was found [43].

The other authors have published the results of the clinical study of PDT with Alasens (FSUE "SSC "NIOPIK", Russia, registration certificate LP-001848 dated September 21, 2012) in the form of intravesical instillation for treatment of superficial bladder cancer. PDT was performed in 45 patients 43 to 75 years old. 25 patients were diagnosed the bladder cancer for the first time, and 20 patients were diagnosed the disease recurrence after previous treatment (17 patients after TUR, and 3 patients after TUR combined with intravesical chemotherapy). PDT was performed once immediately after TUR by combined local irradiation of the tumor bed and diffuse irradiation of the entire bladder mucosa. The follow-up cystoscopy performed 3 months after treatment in all cases showed a complete tumor regression. The dynamic observation after 1 year showed no disease recurrence in 35 (78%) of 45 patients. In 10 (22%) patients the recurrence of bladder tumors 6-12 months after the TUR + PDT + HT was reported. At the same time, 3 patients were diagnosed the disease recurrence after 6 months, 3 patients after 9 months, and 4 patients after 12 months. Re-TUR was performed to these patients [44].

Thus, PDT as an adjuvant therapy in combination with chemotherapy or bladder TUR is a promising method to achieve good results in the treatment of early forms of the bladder cancer.

PDT in the treatment of precancerous lesions and early cervical cancer

The urgency of the problem of the precancerous lesions and early cervical cancer treatment is caused by the high frequency of these diseases in the structure of

gynecological pathology in young women, significantly violating the reproductive function.

Cervical cancer, despite the availability of developed approaches to prevention, diagnosis and treatment, continues to occupy one of the leading positions in the structure of cancer in women. The key role in the cervical carcinogenesis is played by HPV [45].

To date, a large number of scientific works are dedicated to the issue of cervical disease treatment, and a variety of methods for treatment of the background, precancerous lesions and primary cervical cancer was implemented. However, each of these methods has its indications, contraindications, and a number of possible complications: chronic salpingoophoritis exacerbation, bleeding, occurrence of endometriosis, scarring of the uterine cervix, cervical canal stenosis, and impaired reproductive function. Treatment of the background, precancerous lesions and primary cancer should be radical, but at the same time gentle, preserving the anatomical and functional usefulness of the cervix, which largely determines the state of the reproductive system. In this regard, the treatments combining the optimal therapeutic effect without undesired complications listed above are being developed. One of the new approaches to treatment of the cervical disease is a PDT.

PDT method for treatment of cervical pathology has both anti-tumor and anti-viral effect, aimed at both the lesion and the source of the continuous HPV infection of epithelial layers [16].

The study of B. Monk B. conducted the PDT of dysplastic changes in cervical epithelium and preinvasive cancer by topical application with Photofrin with exposure time 24 h and an energy density of 100-140 J/cm^2. 8 of 11 patients (73%) showed a complete regression of pathological changes [46].

There are papers summarizing a quite large amount of the clinical material. The basis of a national study is a comparative analysis of PDT outcome in 195 women with dysplastic changes and early cervical cancer subject to intravenous administration of domestic photosensitizers. All patients were diagnosed with HPV of 16/18 types. The antitumor and antiviral effects after PDT were evaluated. A complete tumor regression in 178 persons, partial regression in 6 patients, and stabilization in 11 patients was diagnosed. The complete eradication of the virus was diagnosed in 182 persons, partial in 8 patients and the lack of effect in 5 patients [16].

Thus, PDT for the precancer and early cervical cancer is an effective organ-preserving method of treatment affecting not only the pathological epithelium, but also the causative factor of cervical carcinogenesis, which allows not only to cure the patient, but also to promote a full medical and social rehabilitation of women. PDT can be considered as a method of secondary prevention of cervical cancer in the virus-positive women and used as an independent treatment method in this group of patients. Photodynamic therapy is an alternative treatment of pretumor and primary tumor cervical pathology preserving the anatomical and functional integrity of the organ, which is important for the women's reproductive function.

PDT in the treatment of degenerative diseases, intraepithelial neoplasia and primary cancer of the vulva

Vulvar cancer ranks fourth in the structure of oncogynecological disease [17]. Its frequency among malignant tumors of the female genital organs is 5-8%. Prevention and treatment of vulvar cancer is a pressing issue of the modern clinical gynecological oncology. Cancer of the vulva is commonly preceded by a variety of background and precancerous diseases. The underlying disease of the vulva are squamous hyperplasia and lichen sclerosus. In recent years, there has been an increase in the number of degenerative diseases of the vulva, lichen sclerosus and vulvar squamous cell hyperplasia, against which, according to different authors, the malignant tumors appear in 9-49% cases [47].

In 20-30% cases, the vulvar cancer is developed in the background of dysplasia. A prolonged conservative treatment of patients with pretumor pathology without morphological verification of the process leads to a delayed diagnosis of the cancer. While the vulvar cancer is a visually accessible form malignant tumors, more than 50% patients arrive at the specialized medical institutions with generalized forms of the disease (2nd or 3rd degree) [7].

Planning and implementation of treatment of patients with pretumor disease and cancer of the vulva is associated with considerable difficulties. The tumor is often located in close proximity to important anatomical structures (urethra, vagina, rectum) or extends to them, which complicates the surgery. The refusal from resection of these anatomical structures significantly worsens the prognosis for the patient. The combination therapy is the most effective. However, in some patients, the combination therapy cannot be performed due to severe comorbidities, excluding any kind of surgery [48]. The possibilities of the vulvar cancer and precancer therapy have widened after introduction of photodynamic therapy into the clinical practice.

The analysis of the literature shows that PDT has become fairly widespread for the background, pre- and primary cancer of the vulva in recent years.

A paper of domestic authors analyzes the results of treatment for patients with degenerative disease of the vulva, which were subjected to PDT using the domestic photosensitizers. The treatment was carried out to 30 patients with vulva lesions. By the nature of the detected pathology of the vulva, lichen sclerosus of the vulva was verified in 20 patients (66,7%), squamous hyperplasia of the vulva is 8 patients (26,6%), and a mixed dystrophy in 2 patients (6,7%). Age of patients ranged from 33 to 80 years old, the mean age being 56.5 years old. A complete clinical remission in the group of vulvar disease was observed in 27 (90%) of 30 patients. 3 (10%) patients with vulvar lichen sclerosus needed a re-PDT, after which the clinical cure was diagnosed. In all cases, a good cosmetic effect was recorded, which is especially important for women of reproductive age [49].

According to another clinical study, the PDT outcome in 67 patients was analyzed. Lichen sclerosus of the vulva was verified in 36 patients (53,7%), a squamous hyperplasia of the vulva in 16 patients (23,9%), and an intraepitelial neoplasia of the vulva of the 1st to 3rd degrees I in 15 patients (22,4%). A complete clinical remission was observed in 59 (88,1%) of 67 patients. 8 (11,9%) patients had a partial remission, which required a re-PDT, after which the clinical cure was diagnosed. PDT of the affected dystrophic process in the vulva area prevented the disease progression and allowed achieving the clinical recovery of 92,5% patients [50].

Analysis of the PDT outcomes using the domestic photosensitizers in the treatment of degenerative diseases and intraepithelial neoplasia of the vulva showed a high therapeutic efficacy with minimal side effects and the lack of complications after treatment. PDT enables the organ-preserving therapy for patients with diseases of the vulva without impairing their quality of life. All this testifies to the high efficiency of this method in the treatment of patients with diseases of the vulva and the prospects for further development of this area in gynecologic oncology.

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