REVIEWS

PHOTODYNAMIC THERAPY OPPORTUNITIES FOR THE TREATMENT OF ERYTHROPLASIA OF QUEYRAT

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Abstract

The review is dedicated to the analysis of the effectiveness of the treatment of erythroplasia of Queyrat (EQ) using photodynamic therapy (PDT). Particular attention is paid to the relationship between EQ and human papillomavirus (HPV) infection. The data of various researchers are presented, confirming the correlation between the development of the EQ and the HPV infection, however, it is noted that due to the small number of studies it is difficult to draw reliable conclusions on the presence and strength of this connection. The mechanisms of PDT involved in the implementation of both the antitumor effect in the treatment of EQ and the antiviral effect against HPV are considered. The data of 12 clinical studies and observations of the results of PDT of the EQ conducted in recent years are analyzed. An analysis of literature data showed that in the treatment of EQ, one of the two photosensitizers is usually used locally: 5-aminolevulinic acid or 5-aminolevulinic acid methyl ester. The treatment parameters in all the analyzed studies were similar: exposure to the ointment for 3–5 hours followed by irradiation with a light dose of 37–105 J/cm^2. The number of PDT courses in different studies varied from 1 to 19. The effectiveness of treatment varied widely in different studies and clinical observations. Most studies have demonstrated high efficacy of PDT with complete regression in 36–83% (100% in one study) and a relapse-free follow-up period of up to 51 months. However, there were also individual clinical observations of patients in whom the treatment with the method of PDT was ineffective. It is possible that the described results were associated with improperly selected regimes of PDT or a large lesion area. Most authors especially note a very good cosmetic effect and a complete absence of scars after the treatment. Thus, PDT is an effective and promising method for the treatment of EQ that requires, however, a more thorough development of the application regimen and a deeper study of the antitumor and antiviral components of the mechanism of action.

Keywords: 5-aminolevulinic acid, aminolaevulinic acid methyl ester, photodynamic therapy, erythroplasia of Queyrat.

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ВОЗМОЖНОСТИ ФОТОДИНАМИЧЕСКОЙ ТЕРАПИИ ПРИ ЭРИТРОПЛАЗИИ КЕЙРА

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Резюме

Обзор посвящен анализу эффективности лечения эритроплазии Кейра методом фотодинамической терапии (ФДТ). Особое внимание уделено вопросам взаимосвязи эритроплазии Кейра с инфицированием вирусом папилломы человека (ВПЧ). Приведены данные исследований, подтверждающие корреляцию между развитием заболевания и инфицированием ВПЧ, отмечено, что в связи с небольшим количеством исследований сложно делать достоверные выводы о наличии и силе этой связи. Рассмотрены механизмы ФДТ, участвующие в реализации как противоопухолевого эффекта при лечении эритроплазии Кейра, так и противовирусного действия в отношении ВПЧ. Проанализированы данные 12 клинических исследований и наблюдений результатов ФДТ при эритроплазии Кейра,

проведенных в последние годы. Установлено, что при лечении заболевания, как правило, используют местно один из двух фотосенсибилизаторов: 5-аминолевулиновую кислоту (5-АЛК) или ее метиловый эфир. Параметры лечения во всех исследованиях были близки: экспозиция мази продолжительностью от 3 до 5 ч с последующим облучением со световой дозой 37 - 105 Дж/см^2. Количество курсов ФДТ в разных исследованиях составляло от 1 до 19. Эффективность лечения широко варьировала в разных исследованиях и клинических наблюдениях. Большинство исследований демонстрировало высокую эффективность ФДТ с полной регрессией образования в 36 - 83% наблюдений и продолжительностью безрецидивного периода до 51 мес. Имелись и отдельные клинические наблюдения, в которых ФДТ оказалась неэффективна. Возможно, описанные результаты были связаны с неправильно подобранными режимами ФДТ или большой площадью поражения. Большинство авторов отмечают хороший косметический эффект ФДТ и полное отсутствие рубцов после проведенного лечения. Таким образом, ФДТ является эффективным и перспективным методом лечения эритроплазии Кейра, однако, требующим тщательной отработки режимов применения и более глубокого изучения противоопухолевого и противовирусного компонентов механизма действия.

Ключевые слова: 5-аминолевулиновая кислота, метиловый эфир 5-аминолевулиновой кислоты, фотодинамическая терапия, эритроплазия Кейра

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Introduction

Penile cancer is a relatively rare pathology. In Western countries, the disease is rare, its frequency being below 1 case per 100,000 men [1]. In the United States, the proportion of penile cancer is from 0.3% to 0.6% of all cancers in men and 2% in the structure of malignancies of the male genitals [2]. Penile cancer is divided into surface forms (erythroplasia of Queyrat, Bowen's disease), which originate from squamose epithelium, are limited to it and do not penetrate the underlying dermis, and invasive tumors (all T categories). Invasive forms are represented by squamous cell carcinoma, which accounts for more than 95% of all cases of penile cancer [2].

Erythroplasia of Queyrat, as a specific clinical process, was first described by L. Queyrat in 1911. In 1912, J.T. Bowen described two cases of precancerous dermatosis, which was later called Bowen's disease. Both terms have been used interchangeably in dermatology and urology for a long time, but currently these are clinically different diseases [3].

Erythroplasia of Queyrat refers to carcinoma in situ (CIS) of the penis characterized by the appearance of a slowly growing shiny bright red plaque with clear borders on the balanus or the inner leaf of the foreskin; the disease is mainly found in senior men. Between 10% and 33% of penile CIS cases progress to invasive squamous cell carcinoma [4].

The connection between erythroplasia of Queyrat and HPV

Many studies state a close correlation between penile CIS and human papillomavirus (HPV) infection. According to the literature, the prevalence of HPV in penile cancer varies from 15% to 71%, depending on the type of tumor and the sensitivity of the virus detection method. HPV is associated with 80 to 100% of cases of basaloid and warty penile cancer, and 33 to 35% of keratinizing and verrucous forms of the disease [5, 6].

The main topic of discussion is the relationship of HPV infection with the risk of progression of erythroplasia of Queyrat to squamous cell carcinoma and the risk of relapse after antitumor treatment if HPV infection remains. The number of studies is limited, which makes it impossible for us to draw reliable conclusions about the presence and the strength of this relationship. However, the connection between primary erythroplasia of Queyrat and HPV infection has been confirmed in many studies [6, 7].

U. Wieland et al. [8], who studied the correlation between erythroplasia of Queyrat and other forms of penile cancer and HPV infection, obtained results that clearly confirm the relationship. The authors found HPV DNA in all patients with erythroplasia of Queyrat and none in the control group of patients with inflammatory penile lesions. HPV type 8 was detected in all tissue samples of patients with erythroplasia of Queyrat, and type 16 was found in 88% of the samples. Half of the surveyed individuals were found to have genital HPV of type 39 and/or 51, with a high carcinogenic risk. It should be noted that all the HPV type 8 DNA nucleotide sequences found in erythroplasia of Queyrat showed some polymorphism among themselves and differed in the specificity of the nucleotide sequence from the reference HPV type 8 sequence. Determination of viral load in patients with erythroplasia of Queyrat by PCR showed that the level of HPV type 16 in biopsies from the pathological focus was 1 to 5 orders of magnitude higher than the level of HPV type 8. In Bowen's disease, HPV type 8 was not detected in the biopsy material.

The study of J. B. Wang et al. also included results confirming the link between HPV infection and penile CIS [9]. The authors found type 16 HPV DNA in 56.9% of cases of squamous cell carcinoma of the external sex organs *in situ*. The test for HPV type 16 DNA was positive in 33.3% of cases of erythroplasia of Queyrat.

The methods of treatment of erythroplasia of Queyrat

For a long time, the leading method of treatment of the disease was surgical. In most cases, penectomy was performed, which is a crippling operation and a strong psycho-traumatic factor for patients, in some cases leading to depression. With this in mind, organ-preserving treatment options were studied in order to improve functional results without reducing patient survival rate. Local application of 5-fluorouracil alone or in combination with other methods can be effective for non-invasive lesions of non-hairy skin areas [10], since there are some reports of clinical observations of secondary progression of the tumor process from hair follicles after treatment [11]. Effective treatment methods also include local simple excision, circumcision for lesions limited to the foreskin, and Mohs micrographic surgery [2, 12, 13]. Laser surgery with carbon dioxide or Nd:YAG [14, 15], cryotherapy [16], and radiotherapy [17] are also used to treat erythroplasia of Queyrat. Recently, 5% Imiquimod cream has been successfully used [18, 19].

Erythroplasia of Queyrat is characterized by high rates of relapse after the use of all the described therapies, which may be associated with participation of HPV in the pathogenes of the disease [3]. Thus, one of the goals of therapy is to target the HPV. Currently, there is no optimal treatment option for HPV-associated penile CIS, in which it is possible to effectively fight both the underlying disease and the HPV infection. Features of the pathogenesis of the disease indicate the feasibility of developing a treatment method that has both antitumor and antiviral effects, which is why photodynamic therapy (PDT) is of particular interest in the treatment of erythroplasia of Queyrat.

The mechanism of the antiviral effect of PDT

The photodynamic antiviral effect does not depend on specific interaction with receptors. This non-specificity of photodynamic damage is one of its advantages. Given the genetic flexibility of viruses (as well as bacteria), this non-targeted mechanism of action is less likely to initiate the development of resistance in viruses [20]. Since photodynamic effects are usually local, the clinical use of photodynamic inactivation is limited mainly to localized viral lesions, such as herpes lesions or warts [21]. Systemic effects of photodynamic treatment have been identified recently that trigger the body's immune response [22-25]. This makes the use of PDT as an antiviral treatment an even more promising method.

The therapeutic effect of PDT on viruses is implemented at the expense of the formation of reactive oxygen intermediate (mostly singlet oxygen) with the activation of the photosensitizer under the influence of light of a certain wavelength.

The localization of the photosensitizer near sensitive molecular targets is extremely important in the implementation of the photodynamic effect. This is due to the short lifetime of singlet oxygen formed in the biological environment, which is measured by microseconds [26]. The specific time of inactivation depends on the location of the photosensitizer, for example, 0.4 ± 0.2 μs near the membranes in living cells [27] or 1.2 ± 0.3 μs in blood vessels [28]. Longer periods of singlet oxygen existence have also been recorded [29]. The distance of intracellular diffusion of singlet oxygen is small relative to the cell diameter. This means that the effect of singlet oxygen generated inside the cell is spatially limited to its immediate environment. However, singlet oxygen generated near the cell membrane may be able to penetrate the membrane.

The size of viruses usually ranges from 0.02 to 0.3 μm, although some very large viruses up to 1 μm are also known. Viruses contain one type of nucleic acid: DNA or RNA, which is bound to a protein shell called a capsid. In complex viruses, the capsid is surrounded by a lipoprotein envelope, which is a structure derived from the membranes of the virus-infected cell. Taking into account the basic structure of viruses, there are three main molecular targets for reactive oxygen intermediates (ROI) generated during the photodynamic reaction: nucleic acids, viral proteins, and viral lipids, if any (Fig.) [22, 30, 31]. The latter are an additional target for ROI, and, consequently, such viruses with a lipid and/or protein shell are usually more sensitive to photodynamic effects [22].

Review of the findings of clinical studies of PDT of erythroplasia of Queyrat

In PDT performed in patients with erythroplasia of Queyrat, the photosensitizer used is usually 5-aminolevulinic acid (5-ALA) or 5-ALA methyl ether [32]. Both 5-ALA and its methyl ether are used locally, in the form of an ointment, which is applied to the affected area as a layer of 1 - 3 mm. The exposure time of the ointment in different studies was from 3 to 5 hours. Almost all researchers noted pronounced pain syndrome in patients during irradiation; the majority of other adverse reactions reported were dysuria, edema of the irradiated tissues and the development of erythema.

The effectiveness of PDT in erythroplasia of Queyrat varies widely in different studies and clinical observations.

A group of researchers from Sweden published the results of a long-term follow-up of 2 patients with eryth-

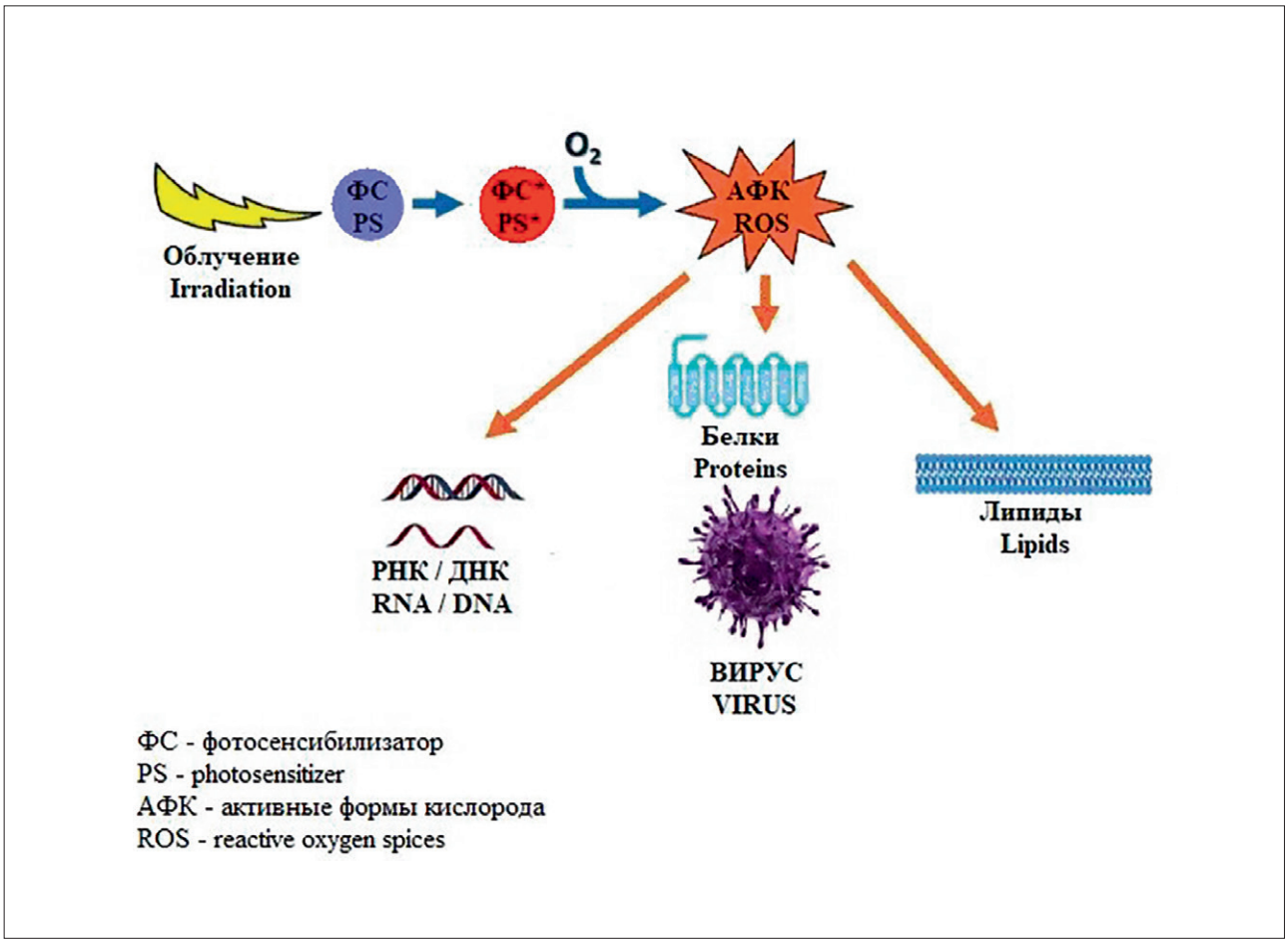

Рис. Мишени фотодинамической инактивации вирусов: нуклеиновые кислоты, белки, липиды
Fig. Targets of photodynamic inactivation of viruses: nucleic acids, proteins, lipids

roplasia of Queyrat after PDT with local application of 20% 5-ALA ointment [33]. One patient was administered 3 courses of PDT, the other, 8 courses. The light dose of each irradiation session was 40-65 J/cm^2, and the power density was 40-65 mW/cm^2. The immediate result of treatment in both patients was evaluated as a complete regression. The follow-up period after treatment was 35 and 40 months. During this time, no recurrence of the disease was registered.

A successful clinical follow-up of a patient with erythroplasia of Queyrat was performed after one course of PDT at P. A. Hertsen Moscow Oncology Research Center [34]. Irradiation was performed once after a 5-hour exposure to the ointment with 5-ALA. The light dose was 150 J/cm^2. The patient was followed up for 1.5 years, with no relapse observed.

Literature provides reports of less successful results of treatment of erythroplasia of Queyrat using PDT with 5-ALA. Researchers from the University Hospital of Wales and the Royal Gwent Hospital (UK) report a clinical follow-up of a patient with erythroplasia of Queyrat after 3 courses of PDT with 20% 5-ALA ointment. The exposure time of the ointment was 4 hours, and the light dose was 105 J/cm^2 [35]. The courses were administered with one month intervals between them. After the third course of PDT, the result was evaluated as a regression of the tumor. However, the researchers noted the occurrence of erythema which remained at the site of irradiation. 4 months after the completion of PDT, on the background of the administration of 5-fluorouracil, a neoplasm was diagnosed at the same place, and a focus of squamous cell cancer was detected during histological examination.

In early 2020 Q.N. Jia et al. reported a clinical follow-up for a patient with erythroplasia of Queyrat who received 2 courses of PDT with 20% 5-ALA ointment. The exposure time to the ointment was 4 hours, the light irradiation dose was 37 J/ cm^2, the irradiation time was 20 minutes [36]. The interval between the courses was 2 weeks. The visit that followed resulted in the discovery of a nodule on the previously treated area of the penis, and the patient was diagnosed with squamous cell cancer based on a histological examination.

There are numerous reports in the literature about the treatment of erythroplasia of Queyrat by PDT with 5-ALA methyl ether.

In 2005, researchers M. R. Lee and W. Ryman [37] described a clinical case of successful use of PDT with 5-ALA methyl ether. Light irradiation was performed after a 3-hour exposure to the cream with 5-ALA methyl ether. The applied layer of cream was 1 mm thick, and 1 g of cream contained 160 mg of the active substance. The radiation wavelength was 630 nm, the light dose was 37 J/cm^2, and the power density was 70 to 100 mW/cm^2. The duration of follow-up was 18 weeks, during which no relapse was detected. Further follow-up was discontinued due to the patient's death unrelated to the principal disease.

P. G. Calzavara-Pinton et al. presented the results of a large-scale retrospective study of the effectiveness of 5-ALA methyl ether in 145 patients with tumor, pre-tumor and infectious diseases treated in 20 dermatological departments and clinics in Italy [38]. In particular, the study evaluated PDT results in 8 patients with erythroplasia of Queyrat. Irradiation was performed after 3-4-hour exposure of the cream with 5-ALA methyl ether (160 mg of the active substance in 1 g of the cream, applied in 1 mm thick layer). The radiation wavelength was 630 nm, and the light dose was 37 J/cm^2. In 5 out of 8 patients, the result of the treatment was evaluated as a complete regression. As the follow-up showed, 2 of these 5 patients later had a relapse.

A group of researchers from Italy presented the results of PDT with 5-ALA methyl ester of erythroplasia of Queyrat in 23 patients [39]. The treatment included 2 courses of PDT with an interval of 1-2 weeks. A cream of 5-ALA methyl ether (160 mg of active substance in 1 g of cream, 1-mm thick layer) was applied to the affected area. The exposure time was 3 hours, after which red light irradiation was performed. The light dose was 37 J/cm^2. Complete regression was obtained in 19 patients, with a follow-up period of 8 to 30 months without relapse (18 months on average). In 3 observations within 3 months after PDT, a relapse of the disease was registered, and 1 patient was found to have fibrosis at the site of irradiation. The cosmetic result in the majority of patients was evaluated as excellent, 4 patients had hyperpigmentation at the PDT site.

Skroza N. et al. report a case of successful PDT treatment with 5-ALA methyl ether in a patient with long-term erythroplasia of Queyrat [40]. A complete clinical response, confirmed by postoperative biopsy, was achieved after 5 weekly courses of treatment. In the course of therapy, moderate edema, erythema and pain were registered within 5 to 7 days after each course of PDT; no problems with urination were observed.

Chinese researchers described the experience of PDT with 5-ALA in 7 patients with erythroplasia of Queyrat [41]. The exposure time of the ointment was from 3 to 5 hours, the light dose: 80-100 J/cm^2, the power density: 60 mW/cm^2. Patients were given from 2 to 7 courses of PDT with an interval of 2 weeks. In 6 out of 7 patients, regression of the pathological process was achieved, while the authors made a special note a good cosmetic effect and complete absence of scars. In 1 case, complete regression could not be achieved due to the initially significant area of the lesion, which spread over 90% of the surface of the penis.

L. Feldmeyer et al. report the results of long-term follow-up of 11 patients with erythroplasia of Queyrat treated with PDT at the University Clinic of Zurich [42]. As a photosensitizer, 5-ALA methyl ether was used in the form of 16% ointment with an exposure time of 3 hours. The light dose for each course of PDT in all patients was 75 J/cm^2. As a result of treatment, 3 out of 11 patients had a complete regression of the tumor, with no relapses during the entire follow-up period of 1.5, 24 and 51 months after the final course of PDT. The number of courses was 19, 7 and 11, respectively, and the interval between them was 1 to 48 weeks.

In 4 patients after 5 to 16 courses of PDT, the immediate effect of treatment was assessed as a partial regression, which persisted for 2 to 45 months with a follow-up period of 4 to 45 months. Later, 2 of these patients were found to have complete regression of the neoplasms after 20 and 45 months of follow-up without any further therapy. In 4 of 11 patients, the progression of the disease was registered after 2 to 4 courses of PDT.

J.Y. Park et al. report the results of clinical observation of a patient with erythroplasia of Queyrat after 10 courses of PDT with 5-ALA methyl ether [43]. The exposure time of the ointment was 3 hours, the light dose was 37 J/cm^2, the power density was 70-100 milliwatt/cm^2. The result of the treatment was estimated as a partial regression. In this connection, treatment with 5% Imiquimod cream was continued. After 4 months, a continued growth of the neoplasm was diagnosed, and a histological examination revealed squamous cell cancer.

A team of Russian authors reports on the experience of successful use of PDT with local application of 5-ALA methyl ether [44]. The patient underwent 2 courses of PDT with an interval of 1 week. The exposure time of the ointment was 3 hours, the light dose, 37 J/cm^2. The result of treatment 3 months after the second course of PDT was evaluated as a complete regression.

Conclusion

Thus, literature describes a significant number of cases of successful treatment of erythroplasia of Queyrat with the use of PDT with 5-ALA and its methyl ester. However, no fundamental studies of the mechanisms of antiviral action against HPV and photocytotoxic action or the assessment of the contribution of these two mechanisms to the overall therapeutic effect in the treatment of this pathology by PDT have been conducted.

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