

MODERN ASPECTS OF PHOTODYNAMIC THERAPY OF BASAL CELL SKIN CANCER

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Abstract

Photodynamic therapy (PDT) is one of the most effective treatments for basal cell skin cancer (BCC). As the incidence rate of BCC is increasing worldwide, interest in developing new methods for diagnosing and treating this disease, taking into account long-term cosmetic results, is growing. The review article presents the results of domestic and foreign studies on the treatment of BCC with PDT. The presented results of studies from various domestic and foreign clinics indicate the high efficiency of independent PDT and a combination of PDT with other treatment methods. PDT is proposed to be used in combination with surgical methods and radiation therapy, immunomodulating and chemotherapeutic agents, and inhibitors of molecules involved in the carcinogenic process. These new strategies open the way to increasing the effectiveness of treatment and prevention of BCC. Moreover, in all studies, the safety of this non-invasive treatment, a low level of adverse reactions during therapy, good tolerance for the patient and excellent cosmetic treatment results are noted. The guidelines currently being developed in Europe and the United States provide consistent expert advice that reflects current published evidence of treatment outcomes for BCC using PDT. Moreover, the recommendations emphasize that the treatment plan for patients with "difficult to treat" BCC should be discussed at an interdisciplinary oncological council.

Key words: basal cell cancer, photodynamic therapy, photosensitizer, photogem, photosens, photoditazine, photolon, aminolevulinic acid.

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СОВРЕМЕННЫЕ АСПЕКТЫ ФОТОДИНАМИЧЕСКОЙ ТЕРАПИИ ПРИ БАЗАЛЬНОКЛЕТОЧНОМ РАКЕ КОЖИ

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Резюме

Фотодинамическая терапия (ФДТ) является одним из наиболее эффективных методов лечения базальноклеточного рака кожи (БКРК). По мере роста показателей заболеваемости БКРК во всём мире всё больше возрастает интерес к разработке новых методов диагностики и лечения данного заболевания с учётом отдалённых косметических результатов. В обзорной статье приводятся результаты отечественных и зарубежных исследований по лечению БКРК с помощью ФДТ. Представленные результаты исследований различных отечественных и зарубежных клиник свидетельствуют о высокой эффективности самостоятельной ФДТ и комбинации ФДТ с другими методами лечения. ФДТ предлагается применять в сочетании с хирургическими методами и лучевой терапией, иммуномодулирующими и химиотерапевтическими агентами, ингибиторами молекул, участвующих в канцерогенном процессе. Эти новые стратегии открывают путь к повышению эффективности лечения и профилактики БКРК. При этом во всех исследованиях отмечается безопасность данного неинвазивного лечения, низкий уровень побочных реакций при проведении терапии, хорошая переносимость для пациента и превосходные косметические результаты лечения. В разработанных в настоящее время в Европе и США руководствах представлены согласованные экспертные рекомендации, отражающие текущие опубликованные доказательства результативности лечения БКРК с использованием ФДТ. При этом в рекомендациях подчеркивается, что план терапии пациентов с трудно поддающимися лечению БКРК должен обсуждаться на междисциплинарном онкологическом совете.

Ключевые слова: базальноклеточный рак кожи, фотодинамическая терапия, фотосенсибилизатор, фотогем, фотосенс, фотодитазин, фотолон, аминолевулиновая кислота.

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Introduction

The incidence of skin cancer is growing widespread in the world [1] in general, as well as the incidence of the most common human cancer such as basal cell skin cancer (BCC) continues to increase [2]. The problem of treating BCC is also relevant for the Russian Federation, which is primarily due to a very high level of incidence. This disease is characterized by a recurrent nature of the course, frequent localization in open areas of the skin with a predominance of facial skin lesions, insufficient effectiveness of existing treatment methods, and significant cosmetic defects. The main methods of treatment of BCC are surgical method, radiation therapy, cryodestruction, immunotherapy, diathermocoagulation [3-12].

Anyway, the above-mentioned methods of treatment have a number of disadvantages: significant side effects, limitations in the case of repeated treatment, not always sufficiently effective and organ-preserving treatment results. Currently, photodynamic therapy (PDT) is one of the most effective, minimally invasive, and organ-preserving methods of treating BCC [3].

A strong inflammatory reaction and PDT-activated immune defense of the body against tumors represent one of the central events in the mechanism of tumor destruction. They include a complex series of interacting specific and nonspecific reactions of different cell types capable of effectively destroying tumor cells by cytolytic and apoptotic mechanisms [13].

In recent years, the PDT method has been actively developed [14]. According to many colleagues, PDT is an effective and safe non-invasive treatment of BCC with excellent cosmetic results. The effectiveness of PDT in BCC is confirmed by extensive studies and clinical trials [15, 16].

PDT in BCC treatment

A group of Russian scientists presented the results of PDT of 139 patients with BCC in their work in 2016. A study of the effectiveness and safety of PDT was conducted using four photosensitizers (FS): photohem, photosense, photolone and photoditazine. It was shown that PDT with the use of chlorin series FS (photolone and photoditazine) provided better long-term results, improving the relapse-free 3-year survival rate up to 90.4% and 92.3%, respectively, compared with 54.7% and 71.1% in

groups in which treatment was carried out using photohem and photosense. At the same time, the authors did not indicate any complications after PDT [17].

In 2019, the PDT subgroup of the steering committee of the European Dermatology Forum prepared a guide that reviewed all current approved protocols and emerging new indications for the PDT use in the treatment of actinic keratosis, Bowen's disease, and BCC. The manual presents agreed expert recommendations reflecting the current published evidence of the PDT effectiveness in the treatment of BCC [18].

Multidisciplinary experts from European Dermatological Forum, European Association of Dermato-Oncology and European Organization of Research and Treatment of Cancer jointly developed recommendations for the diagnosis and treatment of BCC. In accordance with these recommendations, PDT is an effective treatment for superficial and nodular forms of BCC. At the same time, other alternative methods are recommended for the treatment of other forms of BCC. According to the recommendations, the treatment plan for patients with "difficult to treat" BCC should be discussed at the interdisciplinary oncological council [19].

The high efficiency of PDT in the treatment of superficial and nodular forms is indicated by numerous authors [20-23].

K.C. Blanco et al. also showed high efficiency of treatment of superficial and nodular forms of BCC with the use of PDT during a multicenter clinical trial conducted between 2012 and 2014. They also provided the analysis of adverse reactions during and after PDT according to a standardized protocol of the treatment of 866 cases of BCC. In total, 728 patients with a confirmed clinical and histopathological diagnosis of BCC underwent treatment. The size of the tumors was up to 2 cm in diameter. Treatment included curettage and topical application of a cream containing 20% methyl ester of 5-aminolevulinic acid followed by PDT (radiation wavelength was 630 nm, dose rate was 150 J/cm²), which was carried out 3 hours after applying the cream. The intensity of pain sensations during and after treatment was assessed. The intensity correlated with the anatomical localization of the lesion. Patients reported a higher intensity of pain in the lesion focus located on the head and the neck. The pain was less intense on the trunk and the limbs. The

number of sessions also affected the pain reaction. The authors emphasize that PDT occupies a significant place in the treatment of BCC due to its low cost, ease of use and low level of side effects [24].

A number of researchers recommend using PDT in the treatment of BCC if surgical treatment cannot be carried out for some reasons [25–27].

PDT has the advantage of being a non-invasive treatment, providing high efficiency and optimal cosmetic results even though, currently, surgical treatment is most often used in the treatment of this pathology in the world. However, resistant or recurrent tumors may appear, becoming sometimes more aggressive. Therefore, increasing the effectiveness of PDT by combining it with other therapeutic methods is an interesting area of research. Depending on the characteristics and type of tumor, PDT can be used combined with immunomodulatory (imiquimod) and chemotherapeutic (5-fluorouracil, methotrexate, diclofenac, etc.) agents, inhibitors of certain molecules involved in the carcinogenic process, surgical methods, and radiation therapy. These new strategies pave the way to improving the treatment effectiveness and BCC prevention [28].

PDT is an alternative to surgical therapy in the treatment of BCC. Nevertheless, PDT is mainly used in the treatment of superficial tumors nowadays. According to researchers from the University of Bologna, combined treatment in the form of pretreatment of BCC with ablative lasers can increase the effectiveness of therapy. They evaluated a combination therapy using PDT and a CO₂ laser for the treatment of superficial and nodular BCC. In the presented prospective monocentric study, patients with BCC received therapy using a continuous superimpulsive CO₂ laser for the treatment of the nodular form of BCC and a fractional CO₂ laser in the case of the surface form of BCC. Subsequently, all patients underwent PDT using a 5-aminolevulinic acid methyl ester cream and an Atilite CL128® lamp (Galderma). 32 patients (20 men, 12 women) aged 45 to 96 years (a total of 181 foci of BCR) were cured with a CO₂ laser combined with PDT. After 3 months, 100% cure

was achieved, there were no signs of relapse at follow-up from 4 to 18 months in 97.2% of cases. Mild adverse reactions and good aesthetic results were observed. The authors recommend this combination therapy due to its high efficiency, good aesthetic results and a small number of side effects [29].

X. Li et al. also propose the development of combined treatment using PDT. In their study, 8 patients with periorbital BCC received PDT using 5-aminolevulinic acid combined with surgery. After tumor removal (mainly with the preservation of normal skin tissue), each area of the tumor was irradiated using laser radiation with a wavelength of 635 nm and a power density of 177 J/cm² for 15 minutes. In total, 3 PDT courses were conducted during and after surgery. BCC was confirmed by histological examination. The structure of the tumor tissues was studied using transmission electron microscopy, which showed that PDT has an inhibitory effect on the growth of BCC, causing necrosis of tumor cells. Subsequently, there were no relapses during dynamic follow-up for up to 5 years. Patients with infiltrative orbital BCC were able to complete the treatment protocol with good cosmetic results and without significant side effects. The authors note that PDT combined with limited surgical intervention is a safe, effective, and minimally invasive method of treating orbital BCC. At the same time, PDT during and after surgery can help to reduce the volume of surgical intervention [30].

Conclusion

The scope of PDT application continues to expand. Currently, there are quite a lot of data that demonstrate the effectiveness of PDT in the treatment of various forms of BCC. PDT shows high efficiency, good tolerability of therapy by patients and excellent cosmetic results. Considering that pain remains the most common side effect, various effective strategies aimed at reducing pain are currently being developed [31].

Many prospective studies have shown an increase in the effectiveness of the treatment of BCC with the combined use of PDT and other treatment methods.

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