POSSIBILITIES OF PHOTODYNAMIC THERAPY IN THE TREATMENT OF MALIGNANT TUMORS OF THE ORAL CAVITY

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Abstract

Oral mucosa cancer is a common disease with relatively low survival rates. The standard for the treatment of malignant neoplasms (MNO) of the oral mucosa is the surgical method, chemotherapy and / or radiation therapy. With the introduction of modern protocols and the improvement of current treatment methods, the increase in survival is insignificant due to the development of local and distant relapses, the appearance of simultaneous tumors of the oral cavity. Cosmetic and functional results in patients who have undergone complex treatment for oral cancer are often unsatisfactory. There is an obvious need to develop new approaches to treating patients with cancer of the oral mucosa. Photodynamic therapy (PDT) has similar properties.

With the development of endoscopic and fiber-optic equipment, the fields of PDT application have significantly expanded. Foci in the oral cavity and oropharynx became available for PDT. The early stages of oral mucosal cancer are optimal for PDT because large surface defects can be treated with minimal complications. Preservation of subepithelial and collagen structures, which is typical for PDT, promotes healing without the formation of scar processes, thereby achieving an ideal cosmetic and functional effect.

The use of PDT in the treatment of oral cavity cancer is not limited only to the initial stages in an independent version. It is possible to use PDT in combination with surgical and radiation treatment. In case of massive tumor processes, PDT is used for palliative purposes. The influence of the adaptive immune response under the influence of PDT is being studied.

Keywords: photodynamic therapy, squamous cell carcinoma of the oral cavity, dysplasia, precancer, organ-preserving treatment of oral cancer.

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ВОЗМОЖНОСТИ ФОТОДИНАМИЧЕСКОЙ ТЕРАПИИ ПРИ ЛЕЧЕНИИ ЗЛОКАЧЕСТВЕННЫХ ОПУХОЛЕЙ ПОЛОСТИ РТА

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Резюме

Рак слизистой полости рта является распространенным заболеванием с относительно низкой выживаемостью. Стандартом лечения злокачественных новообразований (ЗНО) слизистой полости рта является хирургический метод, химио- и/или лучевая терапия. С внедрением современных протоколов и совершенствованием текущих методик лечения прирост выживаемости незначителен ввиду развития локарегионарных и отдаленных рецидивов, появления симультанных опухолей ротовой полости. Косметические и функциональные результаты у пациентов, перенесших комплексное лечение по поводу ЗНО полости рта, зачастую бывают неудовлетворительными. Очевидна необходимость разработки новых подходов лечения пациентов со ЗНО слизистой полости рта. Подобными свойствами обладает фотодинамическая терапия (ФДТ).

С развитием эндоскопической и оптико-волоконной аппаратуры области применения ФДТ значительно расширились. Стали доступны для воздействия ФДТ очаги в области ротовой полости и рото-гортаноглотке. Начальные стадии рака слизистой ротовой полости оптимально подходят для применения ФДТ, ввиду того что могут быть обработаны обширные поверхностные дефекты с минимальными осложнениями. Сохранение субэпителиальных и коллагеновых структур, что характерно для ФДТ, способствует заживлению без образования рубцовых процессов, благодаря чему достигается идеальный косметический и функциональный эффект.

Применение ФДТ при лечении рака полости рта не ограничивается только начальными стадиями в самостоятельном варианте. Возможно применение ФДТ в комбинации с хирургическим и лучевым методом лечения. При массивных опухолевых процессах ФДТ применяется с паллиативной целью. Изучается влияние адаптивного иммунного ответа под воздействием ФДТ.

Ключевые слова: фотодинамическая терапия, плоскоклеточный рак полости рта, дисплазия, предрак, органосохранное лечение рака полости рта.

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Introduction

More than 300 thousand cases of oral mucosa cancer and about 145.3 thousand cases of death from this type of oncopathology are registered annually in the world [1]. Epidemiological studies in the Russian Federation have shown that in recent decades, disease incidence and mortality from cancer tend to grow steadily [2]. Despite the fact that the loci are located in visually accessible areas, the diagnosis is often made already in the late stages of the disease, in which the average 5-year survival rate does not exceed 5-50% [3]. With traditional methods of treatment of malignant neoplasms (MNO) of the oral cavity, namely surgical and chemoradiation, the rates of recurrence vary from 30 to 47% [4]. In addition, the quality of life after such types of treatment becomes very compromised, due to cosmetic defects and the lack of full rehabilitation (xerostomia, mucositis, fibrosis, osteomyelitis). The question of finding and implementing alternative methods of treatment with minimal side effects remains relevant. Photodynamic therapy (PDT) has similar properties.

Today PDT is a modern organ-preserving method of cancer treatment, as it has a high sensitivity and specificity in the treatment of malignant neoplasms, due to the selective accumulation of a photosensitizer (PS) in tumor tissues. The selectivity of PS accumulation in tumor tissue is due to low cellular pH, high lactate content, low glucose level, abnormal structure of the stroma with extensive interstitial spaces, porous wall of the vasculature, and a large amount of synthesized collagen and lipids.

The antitumor effect of PDT is realized both by necrosis of tumor cells and by indirect action, due to damage to the vessel architecture of the tumor, activation of a nonspecific and specific immune response. PDT induces an apoptotic response bypassing the intermediate pathways of intracellular signaling, which is an advantage in the treatment of multidrug resistant tumors.

With the development of endoscopic and fiber-optic equipment, the fields of PDT application have significantly expanded [5-9].

Loci located in the area of the oral cavity and the oropharynx became available for PDT. The initial stages of the oral mucosa cancer are ideal for PDT, due to the possibility of treating extensive surface defects with minimal complications. The preservation of subepithelial and collagen structures, which is characteristic of PDT, promotes healing without the formation of cicatrical processes, due to which an ideal cosmetic and functional effect is achieved [10].

An important feature of the photodynamic effect is the possibility of simultaneous medical and diagnostic procedures, such as fluorescence diagnostics (fluorescence visualization and spectroscopy).

Fluorescence diagnostics (FD) is based on the ability of tumor cells to accumulate elevated concentrations of endogenous porphyrins and their derivatives, the amount of which increases with the development of pathological processes, as well as other exogenous (administered externally, for example, intravenously) photoactive substances (photosensitizers) and the resulting fluorescence upon irradiation with a certain light wavelengths, and special devices (spectrum analyzers) determine and record the level of fluorescence at certain points. This method makes it possible to assess the level of PS accumulation in tissues and the prevalence of the tumor process. Therefore, the use of FD in oral cancer makes it possible to more accurately diagnose the prevalence of tumor lesions, to identify subclinical lesions [11].

PDT as an independent type of treatment: advantages and disadvantages

Many studies have proven the effectiveness of PDT in the treatment of head and neck tumors (Table 1). It is worth noting the heterogeneity of studies on the treatment of malignant neoplasms of the oral cavity using PDT. The data on the PS used, light sources and radiation doses vary greatly, moreover, the histological type, size and anatomical location are not always clearly described.

One of the first studies on the effectiveness of PDT in malignant head and neck tumors was carried out in 1987 in Chicago at the Illinois Institute of Technology.

The study included 10 patients (11 loci) with primary squamous cell carcinoma of the head and neck and 1 patient with a recurrent form. Photofrin II was used as a PS. At the same time, partial regression was obtained in 8% of cases (1 out of 12 loci) and complete regression - in 83% of cases (10 out of 12 loci) [12].

1987 to 2000 continued experimental and clinical studies on the effectiveness of PDT treatment of oral cancer in an independent variant and in combination with traditional methods of treatment [13-15].

In 2000, at the 5th International Congress on Head and Neck Tumors, the results of the 2nd phase of a prospective non-randomized study on the use of PDT in early stages of oral cancer were presented. The study included 114 patients with stage Tis-T2 oral cavity cancer. Temoporphin was used as a PS at a dosage of 0.15 mg/kg, followed by laser irradiation (20 J/cm^2, intensity 100 mV/cm^2, wavelength 652 nm). When PDT was used on its own, complete regression was obtained in 85% of cases. In 6% of patients in whom partial regression was obtained, then adjuvant therapy was applied, which ultimately made it possible to achieve an overall complete regression figure of 91%. Most cases of complete regression were confirmed morphologically. The median follow-up period was 621 days. The maintenance of complete regression within two years from the moment of treatment was 89% [16].

2000 to 2010 continued active study of the effectiveness of PDT in oral cancer.

A large retrospective study of the effectiveness of PDT in oral cancer was conducted in 2010. Merrill A. Biel. The study included patients who underwent PDT from 1999 to 2008. The total number of patients with initial T1N0 oral cancer was 138. According to the results of treatment, after one course of PDT, all patients showed a complete clinical and morphological response. During the follow-up period up to 211 months (average 99 months), there were seven cases of local recurrence (5%, 131/138). These patients underwent a second PDT session or surgical treatment. During the follow-up process, two patients had regional cancer metastases within 3 months after the end of treatment, which required a lymphadenectomy on the neck. At the same time, the 5-year survival rate in the study cohort was 100% [17].

In a study conducted at the Medical radiological research center named after A.F. Tsyba in 2011, according to the treatment of squamous cell carcinoma of the oral mucosa using PS photolon, complete tumor regression was revealed in 74 of 82 patients. At the same time, PDT was performed in patients with stages T1-T4. The observation period was 3-127 months. Three-year overall survival, regardless of focalization, degree of tumor spread and treatment method, was 85.1 ± 4.8% (73 of 82) [18].

In general, it can be argued that, despite the significant heterogeneity of studies, treatment of the initial stages of oral cavity cancer (T1-T2) is very effective: the full effect is observed in 46-100% of cases (on average 80.7%) and increases in chronological order. It should be noted that the effectiveness of treatment of late stages (T3-4) is lower and amounts to 5-57% (on average 35.25%).

A multicenter study comparing PDT and surgical treatment of early stages of oral cancer T1-T2N0 was conducted in 2013. Sebastiaan A.H. et al. In the PDT treatment group, the total number was 152 patients with 156 foci of squamous cell carcinoma of the oral cavity (T1 - 126, T2 - 30). In the group of surgical treatment - 91 patients and the number of T1 lesions - 58, T2 - 33.

A complete regression was obtained for the PDT group: T1 - 86% (105/126), T2 - 63% (19/30), in comparison with the surgical treatment group 76% (44/58) for T1 and 79% (26/33) for T2, respectively. At the same time, there was no significant difference in PDT and surgical treatment for different T stages. The average follow-up period for patients in the PDT group was 102.6 months for T1 and 113.8 months for T2, 152.7 months and 152.8 months for the surgical treatment group, respectively. Comparative analysis revealed the advantage of surgical treatment for T1 ($p = 0.0084$) and T2 groups ($p = 0.0260$). However, when comparing the overall survival of patients after PDT treatment and the surgical method, no significant difference was found. In conclusion, the authors insist that the treatment of PDT patients using mTHPC as FS and transoral surgery for T1 tumors does not differ significantly. At the same time, in the T2 group, the surgical technique shows slightly better results [19].

A meta-analysis of 24 studies comparing PDT and surgical treatment of early stages of oral cancer showed that a complete regression with PDT was 86%, with a surgical technique 80%. The relapse ratio was 12% and 23%, respectively. Concurrently, there was no statistical difference when comparing the methods [20]. However, surgical interventions are associated with more serious complications and reduce the quality of life compared to PDT.

Considering the results of numerous retrospective studies, it is safe to say that PDT is an effective, alternative method for treating oral cancer. Superficial foci, with a depth of invasion up to 1.0 cm, show the best response with PDT treatment. The main advantages of PDT are minimal invasiveness, organ preservation, excellent cosmetic and functional results, better quality of life, the possibility of repeated use in the same area, without the summation of toxic effects, and a relatively low cost of treatment.

The use of PDT in the treatment of oral cavity cancer is not limited only to the initial stages in an independent version. To improve the effectiveness of treatment, PDT is widely used in combination with traditional methods

Таблица 1
Литературные данные по эффективности ФДТ опухолей головы и шеи
Table 1
Literature data on the effectiveness of PDT of head and neck tumors

Год Year	Фотосенсибилизатор Photosensitizer	Стадия Stage	Кол-во пациентов / очагов (n) Number of patients / lesions (n)	Полный ответ n (%) Full answer n (%)	Время наблюдения (мес) Observation time (months)	Ссылки Links
1987	Фотофрин Photofrin	T1–2	10/12	7 (83)	7–18	[7]
1991	Фотофрин Photofrin	T1	23	20 (87)	8–53	[8]
1996	5-АЛК 5-ALA	SCC	6	1 (17)	76–88	[9]
1997	Темопорфин Temoporfin	T1–2 T3–4	137	6 (46) 4 (57)	6–22	[10]
2000	Темопорфин Temoporfin	T1–2	114	97 (85)	12–60	[11]
2001	Фотофрин Photofrin	T1–2	10	8 (80)	4–115	[12]
2003	Темопорфин Temoporfin	T1–2	25	21 (84)	12–69	[13]
2003	Темопорфин Temoporfin	T1–2 T3	72	7 (100) 1 (50)	6–48 3–12	[14]
2007	Темопорфин Temoporfin	T1–2	20	12 (60)	6–105	[15]
2009	Фотофрин Photofrin	T1	11	10 (91)	7–52	[16]
2010	Фотофрин Photofrin	T1–0	138	131 (95)	8–211	[17]
2011	Темопорфин Temoporfin	T1–2	38	26 (68)	60	[18]
2011	Темопорфин Temoporfin	T3–4	21	1 (5)	21–45	[19]
2011	mTHPC*	T1–2	145	99 (68)	60	[20]
2011	Фотолон Photolon	T1–4	82/86	74 (90)	3–127	[21]
2012	mTHPC*	T1–2 T3–4	47	3 (75) 2 (29)	6–80	[22]
2013	mTHPC*	T1 T2	122/126 30/30	105 (86) 19 (63)	33	[23]
2013	Фотофрин Photofrin	T1–2	18	17 (94)	24	[24]
2013	HPPH*	T1	20	17 (85)	5–40	[25]
2016	Фотофрин Photofrin	T1–2 T3	293	28 (88)	68–158	[26]

*5-АЛК – 5-Аминолевулиновая кислота, mTHPC – Мезо-тетра-гидроксифенил-хлорин, HPPH – пирофеофорбид
*5-ALA – 5-Aminolevulinic acid, mTHPC – Meso-tetra-hydroxyphenyl-chlorin, HPPH – pyropheophorbide.

of treatment. So, for example, after the completion of the surgical stage, a photodynamic effect of the wound surface is carried out to increase ablasticity. It is possible to carry out PDT of the primary focus and surgical treatment in the areas of regional metastasis [21].

The combination of PDT with radiation therapy is an innovative approach. This technique is called "PDT of self-excitating nanoparticles (NPs)" [22]. This approach uses the luminescent properties of NPs. Under the influence of ionizing radiation, NPs emit luminescence, which in turn activates the PS. This technique is provided by an easily reproducible, efficient, low cost method. The synergistic and therapeutic advantages of this technique are manifested in a more pronounced destructive effect when using lower doses of radiation. Radiation therapy has the ability to penetrate deeper than visible light, which is why it is used in the treatment of deep-lying tumors.

Palliative treatment of locally advanced head and neck tumors is possible with PDT using not only remote laser light irradiation, but also with interstitial (intratumoral) irradiation to reduce the volume of massive tumor foci [23]. In this case, it is possible to achieve remission, and/or symptomatic improvement in the form of a decrease in pain, bleeding, and tumor decay.

The influence of PDT on the development of adaptive immunity has been proven. Canti et al. first studied the formation of immune memory after PDT-induced immunostimulation in mice [24]. As a result, immunocompetent mice treated with PDT showed a greater ability to survive after reimplantation of previously isolated tumor cells.

Research is ongoing to improve the specificity of PDT and minimize toxic effects on normal tissues. For more accurate delivery of PSs, the latter were integrated into targeted molecules. One of these methods is the cleavage of PS into monoclonal antibodies (MA) with tumor-assisted antigens that are specifically expressed on cancer cells [25]. Cleavage to MA helps PS to accumulate specifically in tumor cells, avoiding healthy ones. Conjugation of PS with specific antitumor components can achieve the following advantages - improved solubility in aqueous media, deeper and faster tissue penetration, effective elimination of PS from the circulation, and significantly lower nephritic load [26].

In order to achieve higher precision and deeper penetration, PSs that absorb two photons were invented [27]. Two-photon PDT uses ultrafast pulses of infrared light in such a way that two photons of relatively low identical energy are simultaneously absorbed by the PS. Since each photon contributes half of the excitation energy, a longer wavelength is needed to generate oxygen radicals. This allows light to penetrate deeper into the tissue due to lower scattering and absorption [28]. The efficiency of PDT at a depth of up to 2 cm is described [27]. Thus, the specificity of PDT can be improved.

Conclusion

Due to the wide spread of tumor lesions, multifocal growth of foci and frequent relapses, the treatment of superficial forms of oral cavity cancer is a huge problem. In the light of the evidence available from various retro- and prospective studies, it can be concluded that PDT is an alternative method for the treatment of early malignant tumors, both separately and as an adjuvant therapy in combination with other approaches. PDT can also improve the quality of life for inoperable, locally advanced or recurrent tumors.

Together with developments in the delivery of PS and T-vaccines, a deeper understanding of the molecular pathways of cell death, angional mechanisms and their role in the development of the immune response, the most effective treatment protocols based on the PDT technique can be developed. There is a need for randomized clinical trials comparing PDT and standard treatment methods for patients with malignant neoplasms. This will allow PDT to become one of the main methods for the treatment of early lesions, along with the palliative treatment of locally advanced recurrent and refractory head and neck tumors.

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